The Organic Chemistry of Drug Synthesis

VOLUME 2

DANIEL LEDNICER

Mead Johnson and Company

Evansville, Indiana

LESTER A. MITSCHER

The University of Kansas School of Pharmacy Department of Medicinal Chemistry Lawrence, Kansas

A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY AND SONS, New York · Chichester · Brisbane · Toronto

Copyright © 1980 by John Wiley & Sons, Inc.

All rights reserved. Published simultaneously in Canada.

Reproduction or translation of any part of this work beyond that permitted by Sections 107 or 108 of the 1976 United States Copyright Act without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to the Permissions Department, John Wiley & Sons, Inc.

Library of Congress Cataloging in Publication Data:

Lednicer, Daniel, 1929. The organic chemistry of drug synthesis.

"A Wiley-Interscience publication." 1. Chemistry, Medical and pharmaceutical. 2. Drugs. 3. Chemistry, Organic. I. Mitscher, Lester A., joint author. II. Title.

RS421.L423 615'.191 76•28387 ISBN 0•471•04392-3

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

It is our pleasure again to dedicate a book to our helpmeets: Beryle and Betty.

"Has it ever occurred to you that medicinal chemists are just like compulsive gamblers: the next compound will be the real winner."^{*}

^{*}R. L. Clark at the 16th National Medicinal Chemistry Symposium, June, 1978.

Preface

The reception accorded "Organic Chemistry of Drug Synthesis" seems to us to indicate widespread interest in the organic chemistry involved in the search for new pharmaceutical agents. We are only too aware of the fact that the book deals with a limited segment of the field; the earlier volume cannot be considered either comprehensive or completely up to date. Because the earlier book did, however, lay the groundwork for many of the structural classes or organic compounds that have proven useful in the clinic, it forms a natural base for a series that will, in fact, be comprehensive and up to date. This second volume fills some of the gaps left by the earlier work and describes developments in the field up to the end of 1976. More specifically, we have included literature and patent preparations for

those compounds granted a USAN* generic name prior to and including 1976 that did not appear in Volume I.

In assembling the first volume, we faced an apparently staggering mass of material. It seemed at the time that attempts to be inclusive would lead to an undigestible compendium. In order to keep the reader's interest, we chose instead to be selective about material to be included. Specifically, the first volume deals predominantly with organic compounds actually used in the clinic. It is, of course, well known that many compounds die in various stages of clinical trials, either from lack of effect, lack of superiority over existing drugs, or the presence of disgualifying side effects. Particularly since 1962, sponsoring companies have become much more demanding in the standards to be met by a drug before undertaking the cost involved in the clinical work leading to an NDA.[†] For that reason, this period has seen a large increase in the number of compounds that have been granted generic names but have failed to achieve clinical use. Many such failed analogues were omitted from the previous volume. Since we now intend to make the series comprehensive, and since those analogues do have heuristic value, we have chosen to violate chronology and include them in the present volume. Volume 2 thus goes beyond simple updating.

^{*}United States Adopted Name [†]New Drug Application

The organization of the material by chemical classes used earlier has been retained since it provided a convenient method for lending coherence to the subject matter. However, changes in emphasis of research in medicinal chemistry have led us to change the organization of the individual chapters. The small amount of new work devoted to some structural types (e.g., phenothiazines) that formed large units in the earlier book failed to provide sufficient material to constitute a chapter here; what material was available has simply been included under some broader new heading. As was the case previously, syntheses have been taken back to commonly available starting materials as far as possible. An exception to this rule will be found in the section Many of the compounds described are on steroids. corticoids, that are the products of intricate multistep syntheses. In the earlier volume, we described the preparation of some guite highly elaborated corticoids using plant sterols as starting materials. Many of these corticoids are used for preparation of compounds in this volume. Since there seems little point in simply reiterating those sections, a starting material is judged to be readily available if its preparation is described in the first volume. The reference will be to that book rather than to the original literature.

We have endeavored, too, to approach biological activity in the same fashion as we did earlier. The first time some therapeutic indication occurs will be the occasion for a concise simplified discussion of the disease state and the rationale for the specific method of drug therapy. Biological activities are noted for each generic compound at the same time as its preparation. It will be emphasized again that the activities quoted are those given by the authors; this book is not intended as a critical text in pharmacology.

"Organic Chemistry of Drug Synthesis, Volume 2" is addressed to the same audience as was Volume 1: graduate students in medicinal and organic chemistry, as well as practitioners in the two fields. This book also assumes that the reader will have a good understanding of synthetic organic chemistry and at least a rudimentary knowledge of biology.

Finally, we express our sincere appreciation to several individuals who contributed time and talent to this project. Ms. Carolyn Kelly patiently typed the many versions of the manuscript, including the final camera-ready copy, in the midst of the press of her daily responsibilities. Sheila Newland drew the structural formulae, and John Swayze read the entire manuscript and made several useful suggestions to help clarify the text and reduce the number of typos. Ken McCracken and Peggy Williams were extremely helpful in guiding us through the intricacies of the IBM "Office System 6".

Daniel Lednicer Lester A. Mitscher Evansville, Indiana Lawrence, Kansas January, 1980

xii

Contents

Chapter	1.	<pre>Monocyclic and Acyclic Aliphatic Compounds 1. Cyclopentanes a. Prostaglandins b. Other Cyclopentanoids 2. Cyclohexanes a. Cyclohexane and Cyclohexene Carboxylic Acids</pre>	1 1 7 8 8
		 b. Cyclohexylamines c. Miscellaneous 3. Adamantanes 4. Noncyclic Aliphatics References 	12 17 18 20 23
Chapter	2.	Derivatives of Benzyl and Benzhydryl Alcohols and Amines 1. Derivatives of Benzylamine 2. Benzhydrylamine Derivatives 3. Benzhydrol Derivatives References	26 27 30 31 34

Chapter	3.	Phenylethyl and Phenylpropylamines	36
		propylamines	36
		a. Those with a free Aron Group	36
		b. Those Agents With an	00
		Acylated or Alkylated ArOH	
		Group	44
		2. 1-Phenyl-2-Aminopropanediols	45
		3. Phenylethylamines	47
		4. Phenylpropylamines	55
		References	59
Chapter	4.	Arylalkanoic Acids and Their	
		Derivatives	63
		1. Antiinflammatory Arylacetic	
		Acids	63
		2. Diaryl and Arylaikyl Acetic	
		Acids: Anticholinergic Agents	71
		3. Miscellaneous Arylaikanoic	70
		ACIOS	/8 02
		References	02
Chapter	5.	Monocyclic Aromatic Compounds	85
		1. Derivatives of Benzoic Acid	85
		a. Acids	85
		b. Anthranilic Acid and	
		Derivatives	88
		c. Amides	92
		2. Derivatives of Aniline	95
		3. Derivatives of Phenol	98
		a. Basic Etners	98
		D. Phenoxyacelic Acids	TOT
		C. Echers of 1-Aminopropane-	105
		A Arvicultones and Sulfonamides	111
		a Sulfones	111
		h Sulfonamides	112
		5. Functionalized Benzene	
		Derivatives	119
		a. Alkyl Analogues	119
		b. Miscellaneous Derivatives	126
		References	127

Chapter	6.	Steroids	135
-		1. Estranes	136
		2. Androstanes	153
		3. Pregnanes	164
		a. 11-Desoxy Derivatives	164
		b. 11-Oxygenated Pregnanes	176
		References	200
	_		
Chapter	7.	Polycyclic Aromatic and Hydro-	207
		aromatic Compounds	207
		1. Indanes and Indenes	208
		2. Naphthalenes	211
		3. Fluorenes	217
		4. Anthracenes	219
		5. Dibenzocycloheptanes and	
		Dibenzycycloheptenes	221
		6. Tetracyclines	226
		References	228
Chanter	8.	Five-Membered Heterocycles	232
onupoer		1. Derivatives of Pyrrole	233
		2 Derivatives of Furan	238
		3 Derivatives of Imidazole	200
		A Derivatives of Puragole	242
		5 Derivatives of Ovazole and	201
		J. Derivacives of Oxazore and	262
		6 Derivatives of Thiarole	202
		7. Miscellaneous Five-Membered	207
		Heterocycles	270
		References	273
Chapter	9.	Six-Membered Heterocycles	278
		1. Pyridines	278
		2. Piperidines	284
		3. Piperazines and Pyrazines	298
		4. Pyrimidines	302
		5. Miscellaneous Structures	304
		References	308
Chapter	10.	Mornhinoide	314
		l Compounds Derived from	714
		Mornhine	315
		2 Morphinang	373
		2. Hotpittians 3 Benzomornhane	375
		5. Benzomorphans	323

	4. Phenylpiperidines References	328 337
Chapter 11.	Five-Membered Heterocycles Fused to One Benzene Ring 1. Indoles 2. Reduced Indoles 3. Indazoles 4. Benzimidazoles 5. Miscellaneous References	340 348 350 352 354 358
Chapter 12.	 Six-Membered Heterocycles Fused to One Benzene Ring Quinolines Isoquinolines Quinazolines Cinnolines and Quinoxalines Miscellaneous Benzohetero- cycles References 	361 362 373 379 387 387 390 396
Chapter 13.	Benzodiazepines References	401 407
Chapter 14.	 Heterocycles Fused to Two Benzene Rings 1. Central Rings Containing One Heteroatom 2. Benzoheterocycloheptadienes 3. Derivatives of Dibenzolastams 	409 410 420
	 4. Other Dibenzoheterocycles References 	430 432
Chapter 15.	 β-Lactam Antibiotics l. Penicillins 2. Cephalosporins 3. Cephamycins References 	435 437 439 442 443
Chapter 16.	Miscellaneous Fused Heterocycles 1. Compounds with Two Fused Rings 2. Compounds with Three or More	445 446
	Fused Rings	451

	 Purines and Related Hetero- cycles Polyaza Fused Heterocycles Ergolines References 	463 469 475 480
Indexes		483
Cross Index	of Drugs	485
Index		501
Errata for V DRUG SYNTHES	VOLUME 1 of ORGANIC CHEMISTRY OF SIS	513

¹ Monocyclic and Acyclic Aliphatic Compounds

1. CYCLOPENTANES

a. Prostaglandins

When realistic quantities of the natural prostaglandins became available, their extreme potency and wide-ranging biological activities were discovered and visions of therapeutic application in the regulation of fertility, control of ulcers, blood pressure, bronchial asthma, and many other conditions led to a torrent of chemical and biological studies which currently measures about four papers daily, and at least one a week dealing with synthesis alone. Initial chemical emphasis lay in developing efficient syntheses of the natural substances to solve the Presently, the emphasis has shifted supply problem. to preparation of analogues which are intended to be less expensive, more selective in their action, and longer lasting. The five drug candidates in this

section are significant representatives of the hundreds of such analogues available.

The naturally occurring prostaglandins, E_1 , E_2 and A_1 , have potent antisecretory activity when given parenterally and have been suggested for use in treatment of gastric ulcers. Unfortunately, these natural compounds have relatively poor oral activity and rapid metabolism makes their action short-lived. Molecular manipulation proved that an oxygen atom at C_{11} was not necessary for bioactivity but these compounds also lacked the desired oral activity. This problem was solved by a study of the metabolizing enzymes and by borrowing an artifice from steroid chemistry (viz-methyl testosterone, Volume I). The most rapid metabolic deactivating reaction is oxidation to the bioinert C₁₅₋oxo prostaglandins. Converting the latter to a tertiary methyl carbinol led to the desired orally active gastric antisecretory agents.

Starting with 2-carbomethoxycyclopentanone (1), t-BuOK catalyzed alkylation of methyl w-bromoheptanoate gave diester 2 which was then hydrolyzed and decarboxylated. The conjugated double bond was then introduced by a bromination-dehydrobromination sequence to give versatile prostaglandin synthon 3. Esterification to 4 was followed by conjugate addition of sodio nitromethane to give 5. Nitroketone 5 was converted to the sodium salt of the corresponding nitronic acid with sodium in methanol and this was hydrolyzed with icecold dilute H_2SO_4 to ketoaldehyde 6. This sequence is the Nef reaction. Wittig

2

Aliphatic Compounds

reaction of this sodio dimethyl-2-ketoheptyl phosphonate gave 7.^{1,2} Ester hydrolysis to 8 followed by careful reaction with methyl magnesium bromide produced the orally active bronchiodilator, *doxaprost* (9).² *Doxaprost*, at least as originally prepared, is conformationally undefined at C₁₅ and is probably a mixture of R and S isomers.



Enzymic studies demonstrated that the 15dehydrogenase was also inhibited by saturation of the C_{13} double bond and *deprostil* (12) embodies this chemical feature as well.³ Catalytic hydrogenation of 7 produced 10 which was hydrolyzed to 11 and reacted with methyl magnesium bromide in ether. As above, careful control of conditions allowed the organometallic reagent to add selectively to the less hindered side chain carbonyl to produce the orally active potent gastric antisecretory agent, deprostil (12). Interestingly, studies with resolved 12 showed that the unnatural epimer at C_{15} was more potent.



 $\begin{array}{c} (\underline{10}) & R = CH_3, \ R' = 0 \\ (\underline{11}) & R = H, \ R' = 0 \\ (12) & R = H, \ R' = CH_3, \ OH \end{array}$

Introduction of an allene function in place of an olefinic double bond is not commonly employed by medicinal chemists, although such derivatives are occasionally used as progestational steroids. It is interesting, therefore, that the presence of this synthetic feature is consistent with typical prostaglandin biopotency.⁴ In this case, the well-known Corey-lactol synthon, 13, was reacted with dilithio pent-4-yn-1-ol to give acetylenic carbinol 14 which was protected by esterification with acetyl chloride to give 15. Treatment of 15 with LiMe₂Cu led to allene 16. The mechanism of this curious reaction is not clear. Possibly the reagent forms an organometallic derivative of the acetylene moiety with expulsion of the acetate group and double bond migration as a consequence. When this sequence was applied in earlier papers to terminal acetylenes (e.g., J. Am. Chem. Soc., 91, 3289 (1969)), terminal



(13)





(16)

methylation accompanied allene formation and loss of the acetoxy group. Careful alkaline hydrolysis of allene 16 preferentially cleaved the terminal primary The resulting alcohol was then oxidized to ester. the carboxylic acid with Jones' reagent. Saponification under more strenuous conditions removed the remaining acetate group and acid treatment removed the thp ethers. There is thus obtained prostalene (17), which has been described as a bronchodilator and hypotensive agent.

Animal husbandry requires the careful selection and management of breeding stock and a prize stud is an economically valuable asset. The expensive service fee makes it very important that the female be in estrus at the time of mating. In order to

optimize the breeding process, two prostaglandin analogues have recently been marketed which are potent luteolytic agents used to regularize or synchronize estrus in horses. The inclusion of an aryloxy residue in place of the last three carbons of the aliphatic moiety at the methyl terminus of the prostaglandins greatly increases activity and apparently decreases metabolic deactivation.

The synthesis begins with 18, a well-known prostaglandin synthon first developed by Corey.⁵ This is condensed with the appropriate phosphonate ylide reagents (19 or 20) which are themselves prepared by reaction of the appropriate ester or acid chloride of an aryloxyacetic acid with the anion of the dimethyl methylphosphonate. The resulting trans-eneone (21 or 22) is reduced with zinc borohydride, the p-phenylphenylester serving to give preferential reduction to the 15α -ols. The ester is then hydrolyzed with K2CO3/MeOH and the two alcoholic functions are protected as the tetrahydropyranyl ethers. Reduction with diisobutylaluminum hydride at -78°C produces lactols 23 and 24 and their C_{15} epimers. Reaction with the Wittig reagent from 5triphenylphosphonopentanoic acid and acid catalyzed removal of the protecting groups followed by chromatography gives *fluprostenol* (25) and *cloprostenol* (26),⁶ respectively. These compounds are several hundred times more potent by injection than prostaglandin $F_{2\alpha}$ as luteolytic agents, although striking species differences are observed.

6



b. Other Cyclopentanoids

Clinical success with the monoamine oxidase inhibitor and amphetamine analogue tranylcypromine (27) led to an exploration of the effect of ring size on activity.⁷ It was found that an interesting dissociation of properties could be achieved and the best of the series, cypenamine (30), is an antidepressant without significant MAO inhibitory activity. One of the more convenient syntheses⁸ makes use of the finding that hydroxylamine-O-sulfonic acid is soluble in diglyme and therefore is suitable for conversion of organoboranes from hindered and unhindered olefins into the corresponding amines. 1-Phenylcyclopentene



(28) is hydroborated to 29 in the usual way with borohydride and BF_3 . Addition of H_2NOSO_3H followed by acid hydrolysis completes the synthesis of cypenamine (30) with excellent regio and stereospecificity. The reaction sequence is a net cis anti-Markownikoff addition of the elements of NH₂ to 28.

2. CYCLOHEXANES

a. Cyclohexane and Cyclohexene Carboxylic Acids This subgroup is classified strictly for chemical convenience because their pharmacological properties are unrelated to one another.

Clotting of blood is, of course, one of the more significant ways in which the body protects itself from excessive blood loss after injury. After the healing takes place, the clot, which is a three-dimensional polypeptide, is broken down by proteolytic enzymes such as fibrinolysin or plasmin. In some pathological states, fibrinolysis is hyperactive and inhibitors have a hemostatic value.

Plasmin does not occur in free form but is generated as needed from an inactive precursor, plasminogen. The active of plasminogen to plasmin is a proteolytic event and can be inhibited by w-

Aliphatic Compounds

aminocarboxylic acids having a structural or spatial resemblance to lysine. One such agent is p-aminomethylbenzoic acid (33) and its reduction product tranexamic acid (34).⁹ First p-cyanotoluene (31) is oxidized to the carboxylic acid (32) with CrO_3 ; then reduction of the nitrile group with Raney cobalt in the presence of liquid ammonia produces p-aminomethylbenzoic acid (33). Reduction of the aromatic ring of



33 with a platinum catalyst produces mainly the *cis* isomer. Upon heating under nitrogen at $315-325^{\circ}$, isomerization occurs to the *trans*-analogue (34) which possesses all of the hemostatic activity.

Many substances other than estrone possess estrogenic activity and some of these bear only little formal resemblance to the natural hormone. Many years ago, doisynolic acid (39), a steroid degradation product, was shown to have such activity. Over the years many simple compounds have been synthesized following the idea of molecular dissection. One of these is fenestrel (38).¹⁰ Hageman's ester (35) is alkylated to 36 by <u>t</u>-BuOK and ethylbromide. The regioselectivity observed is generally

9



regarded to be a consequence of the greater reactivity of the enolate at C_2 over the other possible enolates (at C_4 and C_6). The double bond is reduced with hydrogen and a palladium catalyst and saponification produces 37 of unspecified stereochemistry. Treatment with phenyl magnesium bromide followed by dehydration with tosic acid in acetic acid leads to the estrogen, fenestrel (38). Presumably, the double bond remains tri- rather than tetrasubstituted in this case because of the steric interactions this latter case would engender between the ethyl and phenyl groups. The stereochemistry of fenestrel is complex so formula 38 implies no stereochemical meaning. A smooth muscle relaxant apparently of the antimuscarinic type whose actions, therefore, are somewhat reminiscent of atropine, is *isomylamine* (43).¹¹ Its synthesis begins with the sodamide catalyzed alkylation of cyclohexyl nitrile (40) with 1-bromo-3-methylbutane and the resulting nitrile (41) is hydrolyzed to the acid (42) with HBr in acetic acid. Alkylation of the sodium salt of this acid using β -chloroethyldiethylamine leads to the desired 43.

Coughing is a useful physiologic device utilized to clear the respiratory tract of foreign substances and excessive secretions. Coughing, however, does not always serve a useful purpose but can rob the patient of sleep. A number of agents are available to suppress this. Many of these are narcotic and have an undesirable abuse potential. One of the agents available which is claimed to be nonnarcotic is *amicibone* (45).¹² The synthesis involves base-catalyzed alkylation of benzyl cyclohexanecarboxylate (44) with β -hexamethyleneiminoethyl chloride a reaction which may go through an aziridinium intermediate.



b. Cyclohexylamines

Although substantial strides have been made toward the chemotherapeutic control of cancer, much remains to be accomplished with respect to broadening of activity spectrum, decreasing host toxicity, increasing remission time, etc., of the various chemotherapeutic agents available. Lacking an all-encompassing rationale upon which to build a drug design program, many potentially useful leads have emerged from directed screening efforts. The nitrosoureas carmustine (BCNU, 48), lomustine (CCNU, 58) and semustine (MeCCNU, 56) are cases in point belonging to the group of cytotoxic alkylating agents.

Cell multiplication requires the rapid synthesis of functional DNA. Those cells which are dividing most rapidly, for example, cancer cells, are particularly sensitive to agents which disrupt this process. The alkylating agents alkylate the purine and pyrimidine bases and so convert them to unnatural compounds. This has the consequence of stopping DNA synthesis and/or inhibiting transcription of the genetic code from DNA. Normal host cells generally spend time in a resting stage where they are less damaged by these cytotoxic agents. Tumor cells, by contrast, are almost always in an active phase of the cell cycle. Following up a lead discovered at the Cancer Chemotherapy National Service Center, it was ultimately shown that unsymmetrical N-nitrosoureas are guite potent alkylating agents and several are now in clinical trial.

BCNU is synthesized^{13,14} by treating phosgene with ethyleneimine without the addition of a base to take up the HCl liberated. Reaction of the intermediate urea (46) in situ with hydrogen chloride serves to open the aziridine rings to afford symbis-2-chlorethylurea (47). This is nitrosated with sodium nitrite in formic acid to give BCNU (48).

On standing in water under various conditions, two main modes of degradation occur and these are rationalized as follows.

The nonnitrosated nitrogen of 49 supplies electrons for an intromolecular displacement of Cl to give intermediate imino ether 50 which collapses to isocyanate 51 and highly reactive 52 which latter fragments, ejecting nitrogen and capturing OH to produce acetaldehyde, after enolization. In the second mode, a cyclic fragmentation process (53) leads to isocyanate 51 and N-hydroxy-2-chloroethylazine (54) which undergoes fragmentation, losing nitrogen and capturing OH (to give 2-chloroethanol) or NH₃ (to give 2-chloroethylamine). As 2-chloroethylamine is a known source of aziridine, this substance has potential alkylating activity. Also, ejection





of nitrogen from 52 to 54 leads to electron deficient species which react with nucleophiles. The isocyanate (51) also adds nucleophiles. Thus, it is not certain at this stage which of these is the most responsible agent for the bioactivity or whether the antitumor properties are a blend of these.

The reader has noted that unsymmetrical ureas can nitrosate on either nitrogen and that these decomposition modes enable one to assign structure to the products. This, in fact, also has preparative significance and both lomustine (CCNU, 58) and its methyl analogue semustine (MeCCNU, 56) are made in this way.¹⁴ In the semustine synthesis, BCNU (48) is decomposed in the presence of two equivalents of trans-4-methylcyclohexylamine to give an 84% yield of unsymmetrical urea 55--probably via the trapping of intermediate isocyanate 51 ($R = CH_2CH_2CI$). Nitrosation with NaNO2/HCO2H produces semustine (56) contaminated with some of the alternate nitroso analogue. Use of cyclohexylamine in this reaction sequence leads to *lomustine* (58) instead. There is some evidence to suggest that in vivo 4-hydroxylation to 59 may be of great importance in the activity of lomustine.



A more complex cyclohexylamine, *tiletamine* (65), is a useful anesthetic in that injection leads to loss of consciousness without an untoward decrease in blood pressure or heart rate and without undue respiratory depression. Its synthesis¹⁵ begins with



bromination of α -thienylcyclopentylketone (60) to give 61. Reaction with ethylamine appears to involve carbonyl addition to 62 followed by epoxy formation (63ab) and then rearrangement to ethylimine 64 after proton loss. It is, of course, apparent that bromide 61 could not undergo a Favorskii rearrangement. Thermolysis of 64 results in a ring expansion and formation of tiletamine (65). The close structural relationship between tiletamine and ketamine¹⁶ is probably not coincidental.

c. Miscellaneous

The molecular dissection embodied in the morphine rule (66) has served as a useful empirical guide for the synthesis of analgesic agents even though a number of significant agents fit the rule poorly. Briefly, the morphine rule suggests that substances containing an aromatic ring attached to a guaternary carbon which is in turn separated from a tertiary amine by two carbons might be active. One such is It is synthesized¹⁷ by reacting the tramadol (69). Grignard reagent prepared from m-methoxybromobenzene (67) with 2-dimethylaminomethylenecyclohexanone (68), itself obtained by Mannich reaction on cyclohexanone, to give tramadol (69). The isomers are separated by fractional crystallization of the HCl salts.



A closely related analgesic which does not fit into the morphine rule is *nexeridine* (73). In this case, ¹⁸ 2-phenylcyclohexanone (70) is reacted with the lithium salt of N,N-dimethylpropionamide (71) to give tertiary alcohol 72. Reduction of the latter with lithium aluminum hydride gives *nexeridine* (73).



3. ADAMANTANES

The adamantane moiety is of medicinal chemical interest because of its inertness, compactness relative to lipid solubilizing character, and symmetry. Considerable interest, therefore, was engendered by the finding that amantadine (78) was active for the chemoprophylaxis of influenza A in man. There are not many useful chemotherapeutic agents available for the treatment of communicable viral infections, so this finding led to considerable molecular manipulation. The recent abrupt end of the National Influenza Immunization program of 1976 prompted a new look at the nonvaccine means for prophylaxis or treatment of respiratory tract infections due to influenza A, especially in that the well-known antigenic shift or drift of the virus obviates usefulness of the vaccine but not amantadine.

The synthesis¹⁹ begins with the halogenation of adamantane (74) with bromine to give 76 or chlorine and AlCl₂ to give 75. The four bridgehead positions

are identical and surprisingly reactive. Reaction



of 76 with acetonitrile in sulfuric acid leads through an apparent SN_1 reaction to amide 77 which is hydrolyzed by base to give amantadine (78). Α similar antiviral agent, rimantadine (83), is also useful for treatment of respiratory diseases due to type A influenza virus. It is synthesized²⁰ from



(81) X = 0(82) X = NOH



adamantyl bromide (76) by AlBr₃ catalyzed addition of vinylbromide to give 79 which is then dehydrohalogenated by heating with KOH to give acetylene 80. Hydration to methyl ketone 81 is achieved by HgO-catalyzed reaction with sulfuric acid. After oxime formation (82) lithium aluminum hydride reduction leads to *rimantidine* (83).

The high lipophilicity of adamantyl moieties suggests that drugs containing them might pass into tissues of high lipid content or cross the bloodbrain barrier. Indeed *carmantadine* (85) is active against the spasms associated with Parkinson's disease. *Amantadine* (78) reacts²¹ with methyl 2,4dibromobutyrate to give ester 84 which can be hydrolyzed with aqueous barium hydroxide to complete the synthesis of *carmantidine* (85).



 $(\frac{84}{85})$ R = CH₃ $(\frac{85}{85})$ R = H

4. NONCYCLIC ALIPHATICS

Many of the biguanides have oral hypoglycemic activity, and metformin (87) is such an antidiabetic agent. Cyanamide has a highly reactive nitrile function because of the electropositive NH₂ group
attached and at pH 8-9 self-adds to form "dicyanamide" (86, for which cyanoguanidine would be a better name). Fusion with dimethylamine²² leads efficiently to metformin (87) by addition to the nitrile function. Metformin is closely related to buformin.²³

The discovery and clinical acceptance of *meprobamate*, and the relative chemical accessibility of this group of compounds has led to intensive exploration of 1,3-biscarbamates. It was found that



substitution of one of the NH hydrogens by an alkyl group changed the emphasis of the biological response from muscle relaxant and anticonvulsant to centrally acting muscle relaxant whose action differs somewhat from meprobamate. Carisoprodol was the best member of one of these series and lorbamate (92) is its cyclopropyl analogue. The chief synthetic problem to be overcome was the differentiation of the two primary alcohol groups of 89, readily accessible by lithium aluminum hydride reduction of the appropriate di-substituted malonate (88). This was solved²⁴ by an ester exchange reaction with diethylcarbonate to give 90 which produced carbamate 91 on reaction with cyclopropylamine. Ester exchange of 91 with ethyl carbamate led efficiently to lorbamate (92), a useful muscle relaxant.



Relatively simple variants of this basic scheme led to the minor tranquilizers *nisobamate* $(93)^{25}$ and *tybamate* (94).²⁶



REFERENCES

- J. F. Bagli and T. Bogri, Tetrahedron Lett., 3815 (1972); for a photochemically-based alternate synthesis, see J. F. Bagli and T. Bogri, J. Org. Chem., 37, 2132 (1972).
- M. Baumgarth, J. Hartin, K. Irmscher, J. Kraemer, D. Orth, H. E. Radunz and H. J. Schliep, Ger. Patent 2,305,437 (1974); W. Lippmann, Prostaglandins, 7, 1 (1974).
- J. F. Bagli, T. Bogri and S. N. Sehgal, Tetrahedron Lett., 3329 (1973).
- P. Crabbe and H. Carpio, J. Chem. Soc., Chem. Commun., 904 (1972).
- 5. E. J. Corey, N. M. Weinshenker, T. F. Schaaf and W. Huber, J. Am. Chem. Soc., 91, 5675 (1969).
- D. Binder, J. Bowler, E. D. Brown, N. S. Crossley, J. Hutton, M. Senior, L. Slater, P. Wilkinson and N. C. A. Wright, *Prostaglandins*, 6, 87 (1974).
- W. R. McGrath and W. L. Kuhn, Arch. Int. Pharmacodyn. Ther., 172, 405 (1968).
- M. W. Rathke, N. Inoue, K. R. Varma and H. C. Brown, J. Am. Chem. Soc., 88, 2870 (1966).
- 9. M. Levine and R. Sedlecky, J. Org. Chem., 24, 115 (1959,); Anon., Spanish Patent 358,367 (1970).
- A. Mebane, U. S. Patent 3,344,147 (1967); A. H.
 Nathan and J. A. Hogg, J. Am. Chem. Soc., 78, 6163 (1956).

- 11. C. H. Tilford, L. A. Doerle, M. G. VanCampen, Jr., and R. S. Shelton, J. Am. Chem. Soc., 71, 1705 (1949).
- A. Frank, A. Kraushaar, H. Margreiter and R. Schunk, Austrian Patent 237,593 (1964).
- 13. H. Bestian, Ann. Chem., 566, 210 (1950).
- 14. T. P. Johnson, G. S. McCaleb and J. A. Montgomery, J. Med. Chem., 6, 669 (1963); T. P. Johnson, G. S. McCaleb, P. S. Opliger and J. A. Montgomery, Ibid., 9, 892 (1966).
- Anon., Netherlands Patent 6,603,587 (1966); C.
 L. Stevens, A. B. Ash, A. Thuillier, J. H.
 Amin, A. Balys, W. E. Dennis, J. P. Dickerson,
 R. P. Galinski, H. T. Hanson, M. D. Pillai and
 J. W. Stoddard, J. Org. Chem., 31, 2593 (1966).
- D. Lednicer and L. Mitscher, Organic Chemistry of Drug Synthesis, 1, 59 (1977).
- 17. Anon., British Patent 997,399 (1965); Chem. Abstr., 63: 9871f (1965).
- B. V. Shetty and T. L. Thomas, Ger. Patent 2,509,053 (1975).
- 19. K. Gerzon, E. V. Krumkalus, R. L. Brindle, F. J. Marshall and M. A. Root, J. Med. Chem., 6, 760 (1963); H. Stetter, J. Mayer, M. Schwarz and K. Wulff, Chem. Ber., 93, 226 (1970).
- 20. P. E. Aldrich, E. C. Hermann, W. E. Meier, M. Paulshock, W. W. Prichard, J. A. Snyder and J. C. Watts, J. Med. Chem., 14, 535 (1971); H. Stetter and P. Goebel, Chem. Ber., 95, 1039 (1962).

- 21. E. H. Gold, U. S. Patent 3,917,840; Chem. Abstr., 84: 59221k (1976).
- S. L. Shapiro, V. A. Parrino and L. Freedman, J. Am. Chem. Soc., 81, 3728 (1959).
- 23. D. Lednicer and L. Mitscher, Organic Chemistry of Drug Synthesis, 1, 221 (1977).
- 24. B. L. Ludwig, L. S. Powell and F. M. Berger, J. Med. Chem., 12, 462 (1969).
- 25. F. M. Berger and B. L. Ludwig, U. S. Patent 2,937,119 (1960); G. Schneider, M. Halmos, P. Meszaros and O. Kovaks, *Monatsh.*, 94, 426 (1963).

² Derivatives of Benzyl and Benzhydryl Alcohols and Amines

As will become apparent in a perusal of this book, organic molecules owe their biological activity to a variety of structural features. Sometimes a set of activities is associated with the structural backbone of a molecule. For example, most prostanoids share certain biological properties despite some changes in functionality; the same will be noted later for Some biological activities are associated steroids. with a specific arrangement of structural subunits; e.g., β -adrenergic blocking agents tend to be derivatives of aryloxypropanolamines. Some activities are quite directly associated with a specific functionality; no better example of this exists than the host of guanidine-containing sympathetic blocking Sometimes, however, no such discernable agents. 26

relationship can be detected between activity and structure. Such classes are often marked by widely divergent activities. Derivatives of benzyl- and benzhydrylamines and alcohols fall into this latter category.

1. Derivatives of Benzylamine In the course of some work aimed at delineation of the structure-activity relationships of the antidepressant monoamine oxidase (MAO) inhibiting drug *pargyline* (1), it was noted that activity was consistent with quite wide modification of the substitution on nitrogen. One of the best drugs to emerge from this study is *encyprate* (4). Hydrogenation of the Shiff base from benzaldehyde and cyclopropylamine (2) gave the secondary amine (3). Treatment of this with ethyl chloroformate afforded the MAO inhibitor *encyprate* (4).¹,²



A derivative of benzylhydrazine, procarbazine (8), exhibits antineoplastic activity. In an interesting insertion-type sequence, reaction of the ptoluamide (5) with ethyl azodicarboxylate leads directly to the substituted hydrazine (6). It is not unlikely that the first mole of the diazo compound oxidizes the benzylic methyl group to an anion or radical anion; addition of that to a second mole of diazo compound would give the observed product (6). Methylation by means of sodium hydride and methyl iodide proceeded at the less hindered amide to give (7). Acid hydrolysis of the carbethoxy groups leads finally to (8).³



An important feature of the antibiotic *chloramphenicol* (9) is the presence of the dichloroacetamide function. Inclusion of this amide in a simpler molecule, *teclozan* (15), leads to a compound with antiamebic activity. Whether this is cause and effect or fortuitous is unclear. The synthesis begins with alkylation of the alkoxide derived from ethanolamine (10) with ethyl iodide to give the aminoether (11). Reaction of α, α' -dibromo-p-xylene (12) with 2-nitropropane in the presence of base leads to dialdehyde (13). The reaction probably proceeds by O-alkylation on the nitropropyl anion followed by bond reorganization and subsequent hydrolysis of the resulting enol ether. Reductive alkylation of the dialdehyde with aminoether (11)gives diamine (14). Acylation by means of dichloroacetyl chloride affords teclozan (15).⁴

The presence of the dichloroacetamide grouping is apparently not an absolute requirement for anti-



amebic activity. In one pertinent example, reductive alkylation of dialdehyde (16) with n-hexylamine affords 17a and Eschweiler-Clark methylation of 17a by heating with formaldehyde in formic acid then leads to the antiamebic drug symetine (17b).⁵



2. Benzhydrylamine Derivatives Attachment of piperazine nitrogen directly to a benzhydryl carbon leads to a pair of compounds which show vasodilator activity, and which should be useful in disease states marked by impaired blood circulation. Reaction of piperonyl chloride (18) with a mixture of piperazine and piperazine dihydrochloride leads to the monoalkylation product (19). (It may be supposed that the mixture of free base and salt equilibrates to the monobasic salt, thus making the second amine less nucleophilic.) Alkylation of 19 by means of benzhydryl chloride then affords the coronary vasodilator medibazine (20).⁶



In an analogous sequence, condensation of piperazine with 4,4'-difluorobenzhydryl chloride gives the monoalkylation product (22). Reaction of 22 with cinnamyl bromide affords flunarizine (23).⁷ Flunarizine is also a coronary vasodilator.



3. Benzyhydrol Derivatives

Cyprolidol (26), a highly modified benzhydrol derivative, is reported to exhibit antidepressant activity; it is of note that this agent bears little structural relation to either the MAO inhibitors or tricyclic antidepressants. Addition of the carbene from



decomposition of ethyl diazoacetate to 4-vinylpyridine gives the cyclopropane (25) (stereochemistry unspecified). Condensation of the ester with phenylmagnesium bromide affords cyprolidol (26).⁸

Basic ethers of benzhydrols are among some of the better known antihistaminic compounds. The earlier volume describes well over a dozen of these drugs. However, research in the area of allergy has recently shifted away from compounds which antagonize the action of histamine to drugs that intervene in earlier stages of the allergic reaction. The basic ethers are therefore represented here by but a few entries. In the preparation of rotoxamine (28). reaction of pyridine-2-carboxaldehyde with the Grignard reagent formed from p-bromochlorobenzene gives the carbinol (27); alkylation with N,N-dimethylchloroethylamine and optical resolution gives rotoxamine (28), the levorotatory form of carbinoxamine.⁹

A slightly more complex scheme is required for preparation of an antihistaminic agent bearing a secondary amine, e.g., tofenacin (32). In the synthesis of tofenacin, alkylation of the benzhydrol (29) with ethyl bromoacetate affords the alkoxy ester (30); saponification followed by conversion to the methylamide gives (31), which is reduced with lithium aluminum hydride to complete the synthesis of 32. 10

Antihistaminic properties are well known to be preserved even when nitrogen is included in a ring, such as in *clemastine* (36). Synthesis of 36 is begun by reaction of 4-chlorobenzophenone (33) with

32



methyl magnesium bromide to give the carbinol (34). Alkylation of 34 with the chloroethyl pyrrolidine (35) then yields *clemastine* (36).¹¹

Arrhythmias, that is, disturbances in the regular timed beating of the heart, often result in life-threatening situations, since the pumping efficiency of the heart is directly related to its rhythmic synchronous contractions. Much activity has thus been expended in searching for drugs which abolish irregularities of the beat without compromising other aspects of cardiac function. One apparently



quite complex compound which exhibits such activity is, in fact, the product of a relatively simple reaction: condensation of cyclopentadiene with bis(2-pyridyl)ketone (37) in the presence of base affords directly *pyrinoline* (38).¹² The condensation can be rationalized by a scheme such as that shown.

REFERENCES

- B. W. Horrom and W. B. Martin, U. S. Patent 3,088,226 (1963); Chem. Abstr., 59: 9888e (1963).
- L. R. Swett, W. B. Martin, J. D. Taylor, G. M. Everett, A. A. Wykes and Y. C. Gladish, Ann. N.

Y. Acad. Sci., 107, 891 (1963).

- 3. Anon., Belgian Patent 618,638 (1962); Chem. Abstr., 59: 6313c (1963).
- 4. A. R. Surrey and J. R. Mayer, J. Med. Chem., 3, 409 (1961).
- 5. K. Gerzon and E. R. Shepard, U. S. Patent 2,759,977 (1956); Chem. Abstr., 51: 3664a (1956).
- Anon., Belgian Patent 616,371; Chem. Abstr., 60: 1767e (1964).
- 7. P. A. J. Janssen, Ger. Offen., 1,929,330 (1972).
- Anon., Belgian Patent 649,145 (1964); Chem. Abstr., 64: 8151c (1966).
- 9. A. O. Swain, U. S. Patent 2,800,485 (1957).
- 10. Anon., Belgian Patent 628,167 (1964); Chem. Abstr., 60: 11942h (1964).
- 11. Anon., British Patent 942,152 (1963); Chem.
 Abstr., 60: 9250g (1963).
- 12. Anon., British Patent 1,009,012 (1965); Chem. Abstr., 64: 3503g (1966).

3 Phenylethyl and Phenylpropylamines

1. PHENYLETHYL AND PHENYLPROPYLAMINES

Those With a Free ArOH Group a. The autonomic nervous system controls tissues and organs whose functions are largely automatic, i.e., not requiring conscious effort for activation. Norepinephrine is the accepted neurotransmitter at the nerve endings and the motor endplate in the sympathetic branch of the autonomic nervous system. Administration of norepinephrine (1) mimics the effect of stimulation of these nerves, causing responses such as vasoconstriction, increased heart rate, relaxation of the ileum, contraction of the uterus in pregnant animals, and relaxation of the lung and bronchial muscles. Synthetic substances eliciting some of these responses are called sympathomimetic agents, and a wide variety are known. More recently, adrenergic agents (another synonym for 36

sympathomimetic agents) have been functionally divided into those acting at α -receptors-- those mainly associated with excitatory processes such as vasoconstriction--and at β -receptors--those mainly associated with inhibitory processes such as vasodilatation. Pharmacological agents which block each of these receptor groups (antagonists) are predominantly used in classifying the drugs. A finer subdivision of the β -receptors into β_1 --which are involved in certain heart muscle and intestinal smooth muscle responses -- and β_2 -- which are involved in certain other smooth muscles such as bronchi. uterus and blood vessels--has been found extremelv useful. Isoproterenol (2) is the archetypal β agonist, having strong activity against both β_1 and β_2 receptors. Generally, the <u>R</u>-configuration at the benzylic carbon is required for maximal potency amongst the agonists and antagonists of this type.



One can infer correctly from the foregoing that increased bulk on the nitrogen generally increases selectivity toward the β -receptors. Further, a

catechol ring or a system electronically equivalent to it is needed for optimum activity, especially at the β -receptors, while alkyl branching in the ethanolamine side chain generally decreases potency.

The chemistry of most of the drugs in this family is quite simple, accounting in part for the very large number of analogues which have been made. The foundation for the chemistry in this series was laid long ago by Stolz^1 in his classic synthesis of the ophthalmic agent *adrenalone* (3) in which he reacted catechol with chloroacetyl chloride and then displaced the reactive chlorine atom with methylamine to complete the synthesis. Borohydride reduction would have given epinephrine (adrenaline).

This process, or simple variants of it, is used to prepare many drugs. For example, one method for the synthesis of *fenoterol* (6), a bronchodilator, starts with sidechain bromination of <u>m</u>-diacetoxy-



38

acetophenone (4) and then displacement of halogen by 1-(p-methoxyphenyl)-2-N-benzylaminopropane to give 5.² Hydrogenation removes the benzyl group, whose function was to prevent overalkylation. Next, HBr cleaves the ether and ester groups, and either catalytic or hydride reduction completes the synthesis of 6. Separation of diastereoisomers was achieved by fractional crystallization.

Analogous methods are used to prepare the ophthalmic agent deterenol (7);³ the bronchodilators clorprenaline $(8)^4$ and isoetharine (9);⁵ the vaso-dilators bamethan $(10)^6$ and ifenprodil (11);⁷ and the smooth muscle relaxant ritodrine (12).⁸



Direct alkylation of the appropriate arylethanolamine is, of course, widely used as, for example, in treatment of ephedrine (13a) with ethyl iodide to give the adrenergic agent, etafedrine (13b),⁹ or with cinnamyl chloride to give the muscle relaxant, cinnamedrine (14).¹⁰ Likewise, alkylation of β -hydroxyphenethylamine with 2-chloropyrimidine gives fenyripol (15), also a muscle relaxant.¹¹

The Mannich reaction can also be used to add an alkyl group in the condensation of ℓ -norephedrine (16) with formaldehyde and <u>m</u>-methoxyacetophenone to give oxyfedrine (17), a coronary vasodilator.¹²



A departure from the catechol pattern of the natural neurotransmitters was achieved following application of the fact that arylsulfonamido hydrogens are nearly as acidic as phenolic OH groups. Nitration of <u>p</u>-benzyloxyacetophenone gave 18 which was reduced to 19 with Raney nickel and hydrazine, and in turn reacted with mesyl chloride to give sulfonamide 20. Methanesulfonate 20 was then transformed to soterenol (21), a clinically useful bronchodilator, in the usual way.¹³ The analogue mesuprine (22) was made by a slight variation in this scheme.¹³ The β blockers sotalol (23) and metalol (24)¹⁴ are made in essentially the same fashion. These agents (23 and 24) owe their activity to their capacity to occupy β -adrenergic receptors without triggering the normal



physiological response. The resemblance of 23 and 24 to the normal agonist helps them serve as antagonists. Greater coverage of β -blockers will be found in Chapter 5.

Amidephrine (25), an adrenergic agent very closely related to metalol, finds use as a bronchodilator.¹⁵ Carbuterol (27), another bronchodilator, is made by reacting 3-amino-4-benzyloxyacetophenone with phosgene to give isocyanate 26. Subsequent treatment of 26 with ammonia produces a urea derivative, which is converted to *carbuterol* by the familiar bromination, amine displacement and reduction sequence.



It is evident that some leeway is available in the substituents tolerable in the <u>m</u>-position. The bronchodilator *sulfonterol (28)* is descended from this observation.¹⁶ Chloromethylanisole (29) is reacted with methylmercaptan to give 30, and the newly introduced group is oxidized to the methylsulfonyl moiety of 31 with hydrogen peroxide. Ether cleavage, acetylation and Fries rearrangement of the phenolic acetate produces 32, which is next brominated with pyrrolidinone hydrobromide tribromide and then oxidized to the glyoxal (33) with dimethyl sulfoxide.



The last reaction perhaps involves an intermediate such as 33a which expells a proton and dimethyl sulfide. Formation of the Schiff's base with tbutylamine, reduction with sodium borohydride and hydrogenolysis of the benzyl ether produces sulfonterol (28). Despite the fact that the methylene hydrogen of sulfonterol must be much less acidic than of the corresponding urea proton on carbuterol or the sulfonamide proton on soterenol, good bioactivity is retained.

That even further leeway is possible is shown by the utility of the saligenin analogue *albuterol* (36) as a bronchodilator.¹⁷ One of the several syntheses starts by Fries rearrangement of aspirin followed by esterification to 34 which is then brominated and reacted with benzyl t-butylamine to give 35. Hydride reduction reduces both carbonyls, and hydrogenolysis of the benzyl group completes the synthesis. Presumably, chelation, believed to be significant in the molecular mode of action of the catecholamines, can still take place with *albuterol*.



b. Those Agents With An Acylated or Alkylated ArOH Group

Once again we come upon a chemical classification that has no pharmacological significance. The three drugs in this small group cause widely different biological responses.

Reaction of the Grignard reagent prepared from m-trifluoromethylbromobenzene (37) with methyl-1,2-dibromoethylether leads to alkoxy bromide 38, which is then reacted with methylamine to give the anorexic agent *fludorex* (39).¹⁸



The gastric anticholinergic agent, elucaine (40), is synthesized by reaction of styrene oxide with diethylamine, followed by esterification with benzoyl chloride.¹⁹ In a similar fashion, eprozinol (44), a bronchodilator, is synthesized by adding the elements of CH_3OBr to styrene, by reaction with t-butylhypobromite in methanol, to give 41. This is next reacted with piperazine to give 42. A Mannich reaction with formaldehyde and acetophenone leads to ketone 43, and reduction with borohydride completes the synthesis of eprozinol.²⁰

2. 1-PHENYL-2-AMINOPROPANEDIOLS

Chloramphenicol was the first orally active, broadspectrum antibiotic to be used in the clinic, and remains the only antibiotic which is marketed in totally synthetic form. Its initial popularity was dampened, and its utilization plummeted when it was found that some patients developed an irreversible aplastic anemia from use of the drug. Of the hundreds of analogues synthesized, none are significantly more potent or certain to be safer than chloramphenicol itself. Two analogues have been given generic names and fall into this chemical classification. It was found early in the game that activity was retained with p-substituents, and that electron withdrawing substituents were best. The synthesis of thiamphenicol²¹ (50) begins with pthiomethylacetophenone (45), which is brominated and then reacted with hexamethylenetetramine to give 46, which is in turn converted to amide 47 by reaction with dichloroacetyl chloride. Reaction with formaldehyde and bicarbonate introduces the hydroxymethyl function of 48, and subsequent Meerwein-Pondorff-Verley reduction with aluminum isopropoxide gives

49. The p-SCH₃ function was oxidized to the methylsulfonyl group of racemic *thiamphenicol* (50) with peracetic acid. The drug has been resolved by saponification of 49, treatment with an optically active acid, reamidation and oxidation. Closely related *cetophenicol* (52) is synthesized from the p-cyano analogue 51 by reaction with methyl lithium followed by amide exchange to give 52.²²



3. PHENYLETHYLAMINES

Phenylethylamines lacking the β -hydroxy group of norepinephrine (1) and related neurotransmitters are much more lipophilic. They exert a much more pronounced central--as opposed to peripheral--sympathomimetic effect. Their action is, however, not direct. It is generally accepted that these agents function at least in part by liberating endogenous catecholamines from storage sites. These, then. exert their characteristic actions. It will be recalled that amphetamine is used clinically for appetite suppression, as an euphoriant-antidepressant, as a nasal decongestant, to improve psychomotor performance, to treat drug depression, in treating children with minimal brain dysfunction (hyperkinesis) and so on. Insomnia, anxiety and, especially with large doses, occasionally psychotomimetic activity are undesirable side effects. Removal of side effects or greater selectivity of action is, as usual, the objective of molecular manipulation in this drug class.

Amphetamine (53) is the prototype drug in this group. One significant objective of molecular manipulation in this group is to retain the appetite depressant activity without significant central stimulation. This is as yet unrealized. Some of the drugs prepared with this purpose in mind are discussed in this section. Reductive alkylation of the nitrogen atom of amphetamine with β -chloropropionaldehyde produces the anorexic agent mefenorex (54).²³ The Schiff's base of amphetamine with chloral, amphecloral (55), is a single molecule combination of a stimulant -anorexic and a sedative.²⁴ Presumably, in vivo hydrolysis releases the sedative, chloral, to combat the excitant action of amphetamine with the intended retention of the anorexic action.



The psychotropic (stimulant) action of amphetaminil (57) may be intrinsic or due to in vivo hydrolysis of the α -aminonitrile function--akin to a cyanohydrin--to liberate amphetamine itself. It is synthesized by forming the Schiff's base of amphetamine with benzaldehyde to give 56, and then nucleophilic attack on the latter with cyanide anion to form amphetaminil (57).²⁵



The alkyl terminus of the side chain need not be methyl for retention of activity. Aletamine (59) is such an agent. It is prepared by the Hofmann rearrangement of α -allyl- β -phenylpropionamide (58).²⁶



The action of monoamine oxidase in terminating the bioactivity of primary amines in this class is inhibited by their conversion to secondary amines, which are not substrates for this enzyme. Greater selectivity of action, for reasons that are obscure, is often seen when a trimethoxyphenyl moiety is present in the drug. Such considerations may have played a role in the design of *trimoxamine* (66), an antihypertensive agent.²⁷ The synthesis starts with trimethoxybenzyl chloride (60), which is alkylated with the anion from ethyl allylacetoacetate and NaH to give 61, which is cleaved to ester 62 with sodium ethoxide via a retro-Claisen reaction. Saponification to acid 63 is followed by conversion to a mixed anhydride by means of ethyl chlorocarbonate. Treatment with ammonia gives amide 64. Hoffman rearrangement with NaOBr gives 65, which is converted to the secondary amine 66 by reaction with ethyl chlorocarbonate, followed by lithium aluminum hydride reduction.



Drugs most often react with biopolymers called receptors in order to exert their pharmacological effects and the receptors are optically asymmetric and should therefore require a most favorable configuration and conformation for maximal activity. Thus, there has been much interest in preparation of rigid analogues both for their utility in mapping receptors and because it was felt that an intrinsically correct fit would maximize intrinsic potency. One drug designed with these considerations in mind is rolicyprine (68), an antidepressant.²⁸ This drug is most probably a latentiated form (prodrug) of the free amine, tranylcypromine (67). Restriction of the primary amino group into a rigid ring system decreases its conformational possibilities enormously. Use of the relatively small cyclopropane ring drastically reduces the potential for deleterious steric bulk effects and adds only a relatively small lipophilic increment to the partition coefficient of the drug. One of the clever elements of the rolicyprine synthesis itself is the reaction of d,l-tranylcypromine (67) with L-5-pyrrolidone-2-carboxylic acid (derived from glutamic acid) to form a highly crystalline diastereomeric salt, thereby effecting resolution. Addition of dicyclohexylcarbodiimide activates the carboxyl group to nucleophilic attack by the primary amine thus forming the amide rolicyprine (68).

Dopamine (69) is a well-known neurotransmitter which interacts with many receptors in the central



nervous system. In Parkinsonism, a fine tremor and muscular rigidity is present which finds its biochemical basis in low levels of dopamine in certain regions of the CNS. Administration of dopamine itself is insufficient to overcome this defect, as it cannot efficiently penetrate the blood-brain barrier. Before the discovery that the corresponding amino acid, DOPA (70), which efficiently entered the brain, was converted enzymatically to dopamine, and thereby constituted effective therapy, various means were employed to attempt such central delivery. One of these used the lipophilicity of adamantoyl analogues. Dopamine was reacted with the acid chloride of adamantane-l-carboxylic acid to give dopamantine (71), an anti-Parkinsonian agent.²⁹

A relatively old compound, p-chlorophenylalanine (74), is able to penetrate the blood-brain barrier into the CNS and serves as a serotonin inhibitor. Interestingly, it increases copulatory behavior in



52

experimental animals, as does testosterone, and has achieved some notoriety on this ground. One of the syntheses begins by diazotization of p-chloroaniline (72), followed by Meerwein reaction with cuprous bromide and acrylic acid to give 2-bromopchlorohydrocinnamic acid (73); which is then reacted with ammonia to give p-chlorophenylalanine (74).³⁰

Dobutamine (76), on the other hand, is a dopamine derivative which does not act centrally, but is of interest because of its coronary vasodilator properties. Such drugs are potentially of value in treatment of angina pectoralis. Further, it is now undergoing extensive clinical trials as an inotropic agent for use in heart failure. Its synthesis is effected by Raney nickel catalyzed reduction of methyl p-methoxyvinylphenylketone (75) to its dihydro analog followed by reductive alkylation with β -(3,4-dimethoxyphenyl)ethylamine. The ether groups are cleaved with HBr to complete the synthesis of 76.³¹



Mebeverine (81), a smooth muscle relaxant, is prepared, *i.a.*, by reacting sodium 3,4-dimethoxybenzoate (77) with 1,4-dichlorobutane to form chloroester 78 which is in turn transformed to the corresponding iodide (79) on heating with NaI in methylethyl ketone. Alkylation of 2-ethylamino-3-p-methoxyphenylpropane (80) with 79 leads to mebeverine (81). 32

Mixidine (84), an amidine related to dopamine (84), has coronary vasodilator properties. It is prepared by reaction of β -(3,4-dimethoxy)phenethylamine (82) with the ethylimino derivative of Nmethyl-2-pyrrolidone (83) in an apparent additionelimination sequence.³³



b. Miscellaneous

Xylamidine (87) is an amidine which serves as a serotonin inhibitor. This agent is prepared by alkylation of m-methoxyphenol with α -chloropropionitrile, KI and potassium carbonate in methylethyl ketone to give 85, which is in turn reduced with lithium aluminum hydride to give the primary amine 86. When 86 is treated with m-tolylacetonitrile in the presence of anhydrous HCl, the synthesis is completed.³⁴ Alternately, one can react primary amine 86 with m-tolylacetamidine under acid catalysis to produce *xylamidine*.



4. PHENYLPROPYLAMINES

The drugs of this group also have widely different pharmacological properties, indicating the general absence of a common pharmacophoric moiety in the group.

Alverine (88) is an anticholinergic agent prepared by reductive alkylation of ethylamine with two equivalents of phenylpropionaldehyde.³⁵

Alkylation of cyclohexylidinephenylacetonitrile (89) with 2-chloroethyldimethylamine, using NaH as base, gives nitrile 90. Note that the product results from alkylation of the enolate which results in a double bond shift. This product (90) is transformed to unsaturated amine 91 on heating with HCl. Catalytic hydrogenation of the double bond then produces gamfexine (92), an antidepressant.³⁶



Reductive amination of methyl 2,2-diphenylethyl ketone (93) with t-butylamine in formic acid leads to terodiline (94), a coronary vasodilator.³⁷

The relationship between serum cholesterol levels and cardiovascular disease remains suggestive, despite intensive research into the subject. In any case, agents which can lower serum cholesterol levels are of therapeutic interest. *Beloxamide* (98),
an N-benzyloxyacetamido derivative, is such an hypocholesterolemic agent. It is synthesized by alkylating N-carbethoxyhydroxylamine with benzyl bromide, using sodium ethoxide. The resulting carbamoyl ester (95) is alkylated again, this time with 3phenylpropyl bromide and sodium ethoxide to give 96, which is then cleaved to the alkylated O-benzylhydroxylamine derivative 97. Reaction with acetyl chloride completes the synthesis of *beloxamide*.³⁸



A propoxyphene-like analgesic which obeys the empirical morphine rule is pyrroliphene (101). A Mannich reaction involving pyrrolidine, formaldehyde and propiophenone gave amino ketone 99, which was converted to tertiary carbinol 100 by reaction with benzyl magnesium chloride; reaction with acetyl



chloride completed the synthesis.³⁴ It is gratifying that *pyrroliphene* (101) retained the desired bioactivity as its synthesis was apparently impelled by the observation that the initial target compounds (e.g., 102) were not very stable chemically.

A somewhat related analgesic, noracymethadol (108), is an active metabolite of acetylmethadol.



It can be synthesized from methyl benzyl 2-chloropropylamine (103) by sodium amide induced alkylation of 2,2-diphenylacetonitrile to give a mixture of amines 104, 105 and 106. Amines 105 and 106 are the expected products of nucleophilic attack on the presumed intermediate asymmetric aziridinium 109. Amine 104 can be rationalized by assuming dehydrohalogenation and rearrangement of the resulting enamine to the charged iminium ion (110) which would rapidly add the nucleophile to give the observed product. In any event, treatment of nitrile 106 with ethyl magnesium bromide, followed by hydrolysis, produced intermediate ketone 107. This was reduced to the secondary carbinol with lithium aluminum hydride and acetylated before catalytic debenzylation of the amine using palladium on carbon catalyst.⁴⁰ Given the nature of the initial alkylation reaction, it is doubtful that this is a practical synthesis.

REFERENCES

- 1. F. Stolz, Chem. Ber., 37, 4149 (1904).
- Anon., Belgian Patent 640,433 (1967); Chem. Abstr., 62: 16124e (1964).
- 3. R. J. Adamski, P. E. Hartje, S. Namajiri, L. J. Spears and E. H. Yen, Synthesis, 2, 478 (1970); J. R. Corrigan, J. Am. Chem. Soc., 67, 1894 (1945).
- 4. J. F. Nash, U. S. Patent 2,887,509 (1959).
- M. Bochmuehl, G. Ehrhart and L. Stein, German Patent 638,650 (1936); Chem. Abstr., 31: 3209⁴ (1937).

- J. R. Corrigan, M. Langerman and M. L. Moore, J. Am. Chem. Soc., 67, 1894 (1945).
- C. Carron, A. Jullien and B. Bucher, Arzneimittelforsch., 21, 1992 (1971).
- P. Claassen, U. S. Patent 3,410,944 (1965); Chem. Abstr., 63: 17965n (1965).
- T. Ueda, S. Toyoshima, K. Takahashi and M. Muraoka, Chem. Pharm. Bull., 3, 465 (1955).
- L. H. Welsh and G. L. Keenan, J. Amer. Pharm. Assn., Sci. Ed., 30, 123 (1941).
- 11. A. P. Gray and D. E. Heitmeier, U. S. Patent 3,274,190 (1966); Chem. Abstr., 66: P18725u (1967).
- K. Thiele, Belgian Patent 630,296 (1963); Chem. Abstr., 61: 1800f (1964).
- 13. A. A. Larsen, W. A. Gould, H. R. Roth, W. T. Comer, R. H. Uloth, K. W. Dungan and P. M. Lish, J. Med. Chem., 10, 462 (1967).
- R. H. Uloth, J. R. Kirk, W. A. Gould and A. A. Larsen, J. Med. Chem., 9, 88 (1966).
- C. Kaiser, D. F. Colella, M. S. Schwartz, E. Garvey and J. R. Wardell, Jr., J. Med. Chem., 17, 49 (1974).
- C. Kaiser, M. S. Schwartz, D. F. Colella and J. R. Wardell, Jr., J. Med. Chem., 18, 674 (1975).
- 17. D. T. Collin, D. Hartley, D. Jack, L. H. C. Lunts, J. C. Press, A. C. Ritchie and P. Toon, J. Med. Chem., 13, 674 (1970); Y. Kawamatsu, H. Asagawa, E. Imamiya and H. Hirano, Japanese Patent 74 70,939 (1974).

- M. Sahyun, Netherlands Patent 6,608,794 (1966); Chem. Abstr., 67: 64023a (1967).
- S. L. Shapiro, H. Soloway, E. Chodos and L. Freedman, J. Am. Chem. Soc., 81, 203 (1959).
- H. E. Saunders, British Patent 1,188,505 (1970); Chem. Abstr., 72: 90466v (1970).
- 21. R. A. Cutler, R. J. Stenger and C. M. Suter, J. Am. Chem. Soc., 74, 5475 (1952); C. M. Suter, S. Shalit and R. A. Cutler, J. Am. Chem. Soc., 75, 4330 (1953).
- 22. M. Von Strandtmann, J. Shavel, Jr., and G. Bobowski, Belgian Patent 638,755 (1964); Chem. Abstr., 62: 11740bc (1965).
- 23. H. Beschke, K. H. Klingler, A. von Schlictegroll and W. A. Schaler, German Patent 1,210,873 (1966); Chem. Abstr., 64: 19486c (1966).
- 24. C. Cavallito, U. S. Patent 2,923,661 (1960); Chem. Abstr., 54: 9846c (1966).
- J. Klosa, German Patent 1,112,987 (1959); Chem. Abstr., 56: 3409d (1962).
- 26. D. D. Micucci, U. S. Patent 3,210,424 (1965); Chem. Abstr., 63: 17897f (1965).
- 27. F. J. McCarty, P. D. Rosenstock, J. P. Palolini,
 D. D. Micucci, L. Ashton, W. W. Bennetts and F.
 P. Palopoli, J. Med. Chem., 11, 534 (1968); F.
 P. Palopoli, D. D. Micucci and P. D. Rosenstock,
 U. S. Patent 3,440,274 (1969); Chem. Abstr.,
 75: 140487n (1971).
- 28. J. H. Biel, U. S. Patent 3,192,229 (1965); Chem. Abstr., 66: 104,804u (1967).

- 29. H. P. Faro and S. Symchowicz, German Patent 2,254,566 (1973); Chem. Abstr., 79: 104963 (1973).
- 30. J. H. Burckhalter and V. C. Stephens, J. Am. Chem. Soc., 73, 56 (1961); G. H. Cleland, J. Org. Chem., 26, 3362 (1961).
- 31. R. Tuttle and J. Mills, German Patent 2,317,710 (1973); Chem. Abstr., 80: 14721z (1974).
- 32. Anon., Belgian Patent 609,490 (1962); T. Kralt, H. O. Moes, A. Lindner and W. J. Asma, German Patent 1,126,889 (1962); Chem. Abstr., 59: 517b (1963).
- 33. G. I. Poos, French Patent 1,576,111 (1969); Chem. Abstr., 72: 132,511p (1970).
- 34. Anon., Netherlands Patent 6,508,754 (1966); Chem. Abstr., 65: 2181e (1962).
- 35. W. Steuhmer and E. A. Elbraechter, Arch. Pharm., 287, 139 (1954).
- 36. M. D. Aceto, L. S. Harris, A. M. Lands and E. J. Alexander, U. S. Patent 3,328,249 (1967); *Chem. Abstr.*, 67: 99834t (1967).
- 37. Anon., British Patent 923,942 (1963).
- 38. B. J. Ludwig, F. Duersch, M. Auerbach, K. Tomeczek and F. M. Berger, J. Med. Chem., 10, 556 (1967).
- 39. A. Pohland and H. R. Sullivan, J. Am. Chem. Soc., 75, 4458 (1953).
- 40. A. Pohland, U. S. Patent 3,021,360 (1962); Chem. Abstr., 56: 3568c (1962).

⁴ Arylalkanoic Acids and Their Derivatives

1. ANTIINFLAMMATORY ARYLACETIC ACIDS

Inflammation is an intimate part of every organism's apparatus for dealing with injuries imposed by the environment. Under normal circumstances, the complex sequence of events characterizing inflammation ceases soon after the environmental challenge stops. Not infrequently, however, the inflammatory process, once started, continues despite the fact that the original triggering event has passed. The incident swelling and pain is familiar to all. Treatment of chronic or persistant inflammation has gone through some clearly recognizable cycles. From about the turn of the century, the standard drug therapy for treatment of this syndrome has consisted of aspirin or another of the simpler aromatics, such as antipyrine and acetaminophen. The layman chooses these materials for self-administration. Use of

these drugs for severe conditions is, however, limited by their relatively low activity--particularly in treatment of the inflammation due to arthritis--and the incidence of side effects when used at higher doses. The discovery of the antiinflammatory activity of cortisone and related corticosteroids quickly led to common prescription of these potent drugs for a wide variety of inflammatory conditions. This widespread use uncovered the host of endocrine effects the corticoids elicit upon chronic administration. This phenomenon required the more selective use of these compounds.

Quite recently, a series of arylacetic acid derivatives has come into clinical use as potent antiinflammatory agents. In general, these compounds show profiles of activity quite similar to *aspirin*, and though as a rule they are more active and are less likely to cause or exacerbate gastric ulcers. Many of these compounds have been shown to be effective in the treatment of arthritis. Since they apparently work by a mechanism different from that of the corticosteroids and are structurally unrelated, they have no corresponding endocrine effects.

An interesting example of this class of nonsteroidal antiinflammatory agents is ketoprofen (5). It is synthesized by reaction of the diazonium salt from amine l with potassium ethyl xanthate, followed by alkaline hydrolysis to afford thiophenol 2. Reaction of the sodium salt of 2 with 2-iodobenzoic acid results in formation of the corresponding bisarylsulfide via nucleophilic aromatic substitution.

64

Friedel-Crafts cyclization of the dibasic acid gives thiaxanthone 4. Note that the symmetry of this intermediate assures formation of a single product. Desulfurization by means of Raney nickel leads, finally, to the antiinflammatory agent, ketoprofen(5).¹



Quite a different route is employed to prepare heterocyclic analogues of 5. For example, acylation of thiophene with p-fluorobenzoyl chloride (6) affords ketone 7. Nucleophilic aromatic substitution with the enolate from diethyl methylmalonate gives the diester 8. Saponification, followed by decarboxylation, gives suprofen (9).^{2,3} A similar sequence starting with the more highly substituted acid chloride (10) affords cliprofen (13).^{2,3}

Structure-activity studies in the phenylacetic acid antiinflammatory series have shown that inclusion of a methyl group on the benzylic carbon usually leads to maximal activity. It is of note that this



group can be replaced, in at least one case, by chlorine. Acylation of phenylcyclohexane with ethyl oxalyl chloride affords the glyoxylic ester 14. Chlorination proceeds meta to the carbonyl group to give 15.⁴ Reduction of the keto moiety gives the corresponding mandelate 16, which reacts in turn with thionyl chloride to replace the hydroxyl group by chlorine to give 17; ester hydrolysis affords fenclorac (18).⁵

In a similar vein, the keto bridge in 5 can be replaced by oxygen with retention of activity. Reduction of acetophenone derivative 19 by means of sodium borohydride leads to the corresponding alcohol (20). Reaction with phosphorus tribromide gives 21. Displacement of the halide with cyanide gives Arylalkanoic Acids



substituted acetonitrile 22, whose saponification affords the antiinflammatory acid, fenoprofen (23). 6



Alclofenac $(26)^7$ represents one of the more extreme simplifications in this class of antiinflammatory agents. The general method for preparation of related compounds⁸ starts with acylation of ochlorophenol to give 24. Alkylation of the phenolic group of 24 with allyl bromide affords the corresponding ether (25). Willgerodt reaction on the acetophenone results in transposition of the side chain and oxidation to the acid to give alclofenac (26).



Inclusion of basic nitrogen in the p-position is also compatible with antiinflammatory activity in this series. Nitration of phenylacetic acid (27) affords 28. Methyl iodide alkylation of the enolate prepared from 28 using two equivalents of sodium hydride gives 29. This appears to involve an Ivanov intermediate (28a). Catalytic reduction of the nitro group leads to the corresponding aniline (30). Acetylation to 31, followed by reaction with chlorine, serves to introduce the desired aryl halogen atom. Removal of the acetyl group, followed by cycloalkylation of the primary aniline (33) with 1,4-dibromo-2-butene affords pirprofen (34).⁹





(<u>28a</u>)

Anthranilic acid derivatives, such as *flufenamic* acid (35), constitute another effective series of non-steroidal antiinflammatory agents. Homologation

of the acid function in that series would of course lead to the arylacetic acid series. It is of note that one such hybrid compound, *diclofenac* (40), does in fact exhibit antiinflammatory activity. In an interesting synthesis, the diphenylamine 36 is first condensed with oxalyl chloride to give the oxanilic acid chloride 37. Friedel-Crafts cyclization under quite mild conditions gives the isatin 38. Reduction of the keto group by means of the Wolff-Kishner reaction gives lactam 39, whose hydrolysis affords *diclofenac* (40).¹⁰



70

2. DIARYL AND ARYLALKYL ACETIC ACIDS: ANTI-CHOLINERGIC AGENTS

Acetylcholine is the neurotransmitter amine of the parasympathetic autonomic nervous system. A host of bodily responses, such as gastric secretion, intestinal motility, and constriction of the bronchi, depend on cholinergic transmission. Ouite some time ago it was discovered that responses due to activation of the cholinergic system can be antagnoized by atropine (41). Experience with this natural product foreshadowed the shortcomings of most subsequent anticholinergic drugs. That is, these agents, as a class, show little selectivity for a given organ system. They tend to ablate all responses mediated by the parasympathetic nervous system. This lack of selectivity leads to a set of side effects, such as dryness of the mouth, blurred vision, and CNS effects, which are guite predictable as extensions of the pharmacology. As has been detailed elsewhere, numerous SAR studies have reduced the requirements for anticholinergic activity to an ester of a benzilic acid with an alcohol related to ethanolamine; esters of cyclic aminoalcohols tend to be more active than the acyclic counterparts.

Clinical trials of some of the more potent tertiary amines revealed these to exhibit marked psychotomimetic activity.¹¹ Much subsequent work thus dealt with the quaternary salts which do not reach the central nervous system. Many of the uses of anticholinergic drugs involve "topical" application (e.g., interior of the stomach, intestine or bronchi);

71

the drugs could thus in principle show a clinically useful effect without first being absorbed parenterally. In addition, quaternization, while greatly inhibiting absorption, should assure that the drug will not cross the blood-brain barrier.

Preparation of the quaternary anticholinergic agent benzilonium bromide (47) is begun by conjugate addition of ethylamine to methylacrylate, giving aminoester 42. Alkylation of 42 with methyl bromoacetate leads to diester 43, which is transformed into pyrrolidone 44 by Dieckmann cyclization, followed by decarboxylation. Reduction of 44 by lithium aluminum hydride leads to the corresponding aminoalcohol (45). Transesterification of alcohol 45 with methyl benzilate leads to 46. Benzilonium bromide (47) is obtained by alkylation of ester 46 with ethyl bromide.¹²

In a similar sequence, reaction of ketoester 52 with 2-thienylmagnesium bromide gives a modest yield of the benzilic ester 53. Transesterification of this with aminoalcohol 51, prepared analogously to 45 by starting with methylamine, gives, after quaternization with methyl bromide, heteronium bromide (54).¹²

Similarly, lactam formation of diethyl glutamate (55) leads to ethyl pyroglutamate (56). Reduction by means of lithium aluminum hydride gives the aminoalcohol 57, which is then N-methylated to give 58. Treatment with thionyl chloride leads to the chloroamine 59 and displacement of halogen (possibly via an aziridinium intermediate) with sodium benzilate





affords poldine (60).¹³ Alkylation of 60 with dimethyl sulfate gives poldine methylsulfate (61), in which the two-carbon bridge between quaternary N and O is preserved by placing a methylene in the position of the pyrrolidine nucleus.



Benzilate esters of piperidinols, as well as those of acyclic aminoalcohols, show similar anticholinergic activity. For example, ester interchange between methyl benzilate and N-methyl-4-piperidinol, followed by quaternization of the resulting ester with methyl bromide, gives *parapenzolate bromide* (62). ¹⁴ In analogous fashion, ester interchange between methyl benzilate and N-ethyl-N-n-propylethanolamine yields *benapryzine* (63). ¹⁵



Biological activity in this series shows considerable tolerance for modification in the ester moiety as well. Esters in which one of the aromatic rings is fully reduced still show good anticholinergic activity. One such agent, propenzolate (66), is prepared by displacement of halogen from N-methyl-3-chloropiperidine (64) by the sodium salt of acid 65. ¹⁶



In yet a further variation on this scheme, the basic center in the molecule can be present as an

amidine. In the synthesis of oxyphencyclimine (69), reaction of chloroacetonitrile with methanol and hydrogen chloride leads to the corresponding iminoether 67. Condensation of 67 with N-methyl propylenediamine gives the corresponding tetrahydropyrimidine (68). Displacement of the halogen with the sodium salt of 65 affords oxyphencyclimine (69).¹⁷



Omission of the hydroxyl group and one of the cyclic hydrocarbons from the acid moiety is apparently not inconsistent with biological activity. Thus, the ester from 2-phenylbutyryl chloride and diethylaminoethoxyethanol, *butamirate* (71), shows antispasmodic activity. In analogous fashion, reaction of the acid chloride from 72 with N-methyl-4piperidinol, followed by quaternization, gives *pentapiperium methylsulfate* (73).¹⁸

Apparently, minor chemical modifications of the benzilcarboxylic acid containing molecules led to a compound which shows surprising analgesic activity. Condensation of N-methylphenethylamine 74 with



ethylene oxide gives aminoalcohol 75; which is then



converted to the halide (76) by means of thionyl chloride. Reaction with methylamine leads to the key diamine 77. Acylation of the diamine with chlorodiphenylacetyl chloride (to 78), followed by displacement of the benzylic halogen by sodium ethoxide, affords the analgesic agent *carbiphene* (79).¹⁹

3. MISCELLANEOUS ARYLALKANOIC ACIDS

It has been known for some time that thyroxine, and related compounds such as *liothyronine (88)* are effective in lowering serum cholesterol. The normal metabolic activity of this class of thyroid active compounds has precluded their use as hypocholesterolemic agents.



78

A program aimed at preparation of analogues of thyroxine which would maximize their effect on lipids resulted in the preparation of thyromedan (87). This agent, interestingly, proves also to have good thyromimetic activity. In the synthesis of 87, reaction of the substituted phenylacetate 80 with tosyl chloride leads to the corresponding tosylate (81). Reaction of that intermediate with the salt from phenol 82 results in aromatic nucleophilic displacement of the highly activated tosylate to afford the diphenyl ether 83. The nitro groups are then reduced catalytically to give diamine 84. Diazotization, followed by Sandmeyer reaction with sodium iodide, affords the desired triiodo intermediate 85. Saponification affords the acid (86), and reaction of the sodium salt of the acid with 2-chlorotriethylamine gives thyromedan (87).²⁰

A highly-substituted phenylacetic acid derivative shows activity as a shortacting narcotic and as an injectable general anesthetic. This agent, *propanidid* (90), is obtained by alkylation of phenol 89 with N,N-diethylchloroacetamide.²¹



Clofibrate (91) has been in clinical use for several years as a serum triglyceride lowering agent. This drug is an important hypocholesteremic

agent also, blocking cholesterol biosynthesis. Appearance of this agent on the market occasioned intensive work in many laboratories aimed at discovering additional compounds with this activity. A distantly related analogue, halofenate (98), was, in fact, found to be effective. In addition, however, clinical trials revealed this analogue to have marked concomitant uricosuric activity; that is, the drug promotes excretion of uric acid. In order to synthesize halofenate, acid 92 is first converted to the acid chloride by means of thionyl chloride; bromination affords the α -halo derivative 93. This is then allowed to react with methanol to give the corresponding methyl ester (94). Displacement of bromine with the anion from meta-trifluoromethylphenol leads to ester 95. The ester is then hydrolyzed and



the product (96) is converted to the acid chloride (97). Acylation of N-acetylethanolamine with 97 yields halofenate (98).²²

A disubstituted butyramide, *disopyramide*, distantly related to some acyclic narcotics interestingly shows good antiarrhythmic activity. Alkylation of the anion from phenylacetonitrile with 2bromopyridine yields 99. Alkylation of the anion from the latter with N,N-diisopropyl-2-chloroethylamine leads to the amine 100. Hydration of the nitrile in sulfuric acid affords *disopyramide* (101).²³



Finally, reaction of the half acid chloride of malonate 102 with N,N-diethylethylenediamine gives the muscle relaxant fenalamide (103).²⁴



REFERENCES

- D. Farge, M. N. Messer and C. Moutonnier, U. S. Patent 3,641,127 (1972); Chem. Abstr., 68: 524 (1968).
- P. A. J. Janssen, G. H. P. Van Daele and J. M. Boey, German Patent 2,353,375 (1974).
- P. G. H. Van Daele, J. M. Boey, V. K. Sipido, M. F. L. De Bruyn and P. A. J. Janssen, Arzneimittelforsch., 25, 1495 (1975).
- D. Julius and N. J. Santora, U. S. Patent 3,321,267 (1971).
- D. Julius and N. J. Santora, German Patent 2,122,273 (1972).
- 6. M. S. Winston, U. S. Patent 3,600,437 (1971).
- 7. N. P. BuuHoi, G. Lambelin and C. Gillet, South African Patent 68 05,495 (1969); Chem. Abstr., 71: 101,554e (1971).
- G. Gariraghi, S. Banfi, U. Cornelli, M. Pinza and G. Pifferi, *Il Farmaco, Ed. Sci.*, 32, 286 (1977).

- 9. R. W. J. Carney and G. DeStevens, German Patent 2,012,237 (1970).
- A. Sallman and R. Pfister, German Patent 1,815,802 (1969).
- 11. R. W. Brimbelcombe, Advances in Drug Research, 7, 165 (1973).
- W. Ryan and C. Ainsworth, J. Org. Chem., 27, 2901 (1962).
- F. F. Blicke and C.J. Lu, J. Am. Chem. Soc., 77, 29 (1955).
- 14. J. Klosa and G. Delmar, J. Prakt. Chem., 16, 71 (1962).
- M. D. Mehta and J. G. Bainbridge, U. S. Patent 3,746,743 (1973).
- 16. J. H. Biel, U. S. Patent 2,995,492 (1957).
- 17. J. A. Faust, A. Mori and M. Sanyun, J. Am. Chem. Soc., 81, 2214 (1959).
- H. Martin and E. Habicht, U. S. Patent 2,987,517 (1961).
- J. Krapcho and C. F. Turk, J. Med. Chem., 6, 547 (1963).
- B. Blank, F. R. Pfeiffer, C. M. Greenberg and J. F. Kerwin, J. Med. Chem., 6, 560 (1963).
- 21. R. Hiltmann, H. Wollweber, F. Hoffmeister and W. Wirth, German Patent 1,134,981 (1962); Chem. Abstr., 58: 4480f (1963).
- 22. W. A. Bolhofer, U. S. Patent 3,517,050 (1970).
- J. W. Cusic and H. W. Sause, U. S. Patent 3,225,054 (1965).

24. P. Galimberti, V. Gerosa and M. Melandri, U. S. Patent 3,025,317 (1962); Chem. Abstr., 56: 550c (1962).

5 Monocyclic Aromatic Compounds

The benzene ring per se does not impart any particular pharmacological response to a drug. It is widely held that its planarity, its ability to bind to tissue receptors by Van der Waals and charge transfer mechanisms, and, particularly, its ability to serve as a conductor of electrons within a substance serve as modulators, enhancing or diminishing the intensity of response to a molecule that is otherwise inherently bioactive.

- 1. DERIVATIVES OF BENZOIC ACID
- a. Acids

Salicylic acid analogues are often active as nonsteroidal antiinflammatory agents because they interfere with biosynthesis of prostaglandins. *Diflunisal* (3) appears to be such an agent. It is synthesized from the nitrobiphenyl *I* by catalytic reduction to



the aniline, diazotization, and heating in aqueous acid to give phenol 2. This is carboxylated using K_2CO_3 and carbon dioxide to give *diflunisal*.¹ Alternatively, the corresponding anthranilic acid derivative 4 is diazotized, then hydroxylated by heating in dilute sulfuric acid to give *diflunisal*.²



Many benzenesulfonamides have diuretic properties, particularly those having two such functions situated meta to one another. To some extent a carboxyl group can serve in place of one of the sulfonamido groups. Bumetanide (8) is such a substance. Chlorosulfonation of p-chlorobenzoic acid leads to 5, which is nitrated, and then converted to sulfonamide 6 with ammonia. The chloro group of 6 is now highly activated toward nucleophilic aromatic substitution, facilitating reaction with phenoxide. Subsequent catalytic reduction in the presence of LiOH produces amino acid Next, treatment with butanol and sulfuric acid 7. not only forms the butyl ester but monoalkylates the amino function. Saponification of the ester group leads to *bumetanide* (8), a diuretic agent possessing 40-fold greater activity in healthy adults than furosemide.³

Tibric acid (10), interestingly, has the mcarboxysulfonamido functionality but its activity is expressed, instead, as suppression of serum triglyceride levels. In its reported preparation, chlorosulfonic acid treatment converts 2-chlorobenzoic acid to chlorosulfonate 9, which readily forms the hypolipidemic agent *tibric acid* (10) on reaction with 3,5-dimethylpiperidine.⁴



b. Anthranilic Acid and Derivatives N-Aryl anthranilic acids are frequently found to have antiinflammatory activity and have been studied extensively to maximize potency and decrease side effects (gastric irritation, ulcers, etc.). These compounds are often synthesized by reacting an orthohalobenzoate salt with a suitably substituted aniline. This procedure failed, perhaps because of steric hindrance, in attempting to synthesize meclofenamic acid (16).⁵ The successful synthesis begins by



treating 2-methyl-4-hydroxy acetophenone (11) with NaOCl, which both ortho-chlorinates adjacent to the phenolic OH and effects a haloform reaction. Decarboxylation leads to the chlorinated meta cresol 12. When 12 is converted to its sodium salt with NaH in DMF

88

and then treated with 2,4-dichloroquinazoline (13), two molecules of the phenol react with the heterocycle to give the nucleophilic aromatic substitution product 14. When heated, 14 undergoes an O to N-aryl rearrangement (Chapman Rearrangement) to give 15. Upon saponification, carbon dioxide and 2,5-dichloro-3-methylaniline are lost and meclofenamic acid (16) results. Reaction of sodium meclofenamate with ethylchloromethyl ether in acetone gives etoclofene (17), which is also active as an antiinflammatory agent. Etoclofene reportedly causes less gastrointestinal irritation than meclofenamic acid to which it is presumably converted after passage through the stomach.⁶



One of the mainstays in the treatment of tuberculosis is paraaminosalicylic acid (PAS). It is not, however, a pleasant drug to take. Phenyl aminosalicylate (20) was synthesized from 4-nitrosalicylic acid (18) by esterification of its acid chloride with phenol to give 19, which is converted to the desired product (20) by reduction with Raney nickel catalyst.⁷ Phenyl aminosalicylate was intended to be more acceptable to patients than PAS.

Unquestionably, the most frequently used analgesic is *aspirin*. The reader will recall that *aspirin* is

regarded as a latentiated form of salicylic acid and is intended to minimize as far as possible the irritation of the gastrointestinal tract that salicylic acid would otherwise cause. Salsalate (24) represents another approach to this problem in which selfesterification has been used to serve the same purpose. Direct self-condensation is difficult to control, although low temperature treatment of salicylic acid with PCl, does work. A more stepwise procedure involves the condensation of benzyl salicylate (21) with the acid chloride of salicylate benzyl ether 22 to produce protected dimer 23. Catalytic hydrogenolysis removes the benzyl groups and completes the preparation of salsalate (24).⁸









Esterification of certain aromatic acids with β -aminoethanol and propanol derivatives frequently results in molecules that show local anesthetic

activity; and some of these derivatives also have an antiarrythmic action on the heart. Amoproxan (27) is such an agent. It can be synthesized by reacting epichlorohydrin with 3-methylbutanol and BF₃ to give epoxide 25. This, then, is reacted with morpholine to give alcohol 26, which is then reacted with 3,4,5trimethoxybenzoyl chloride to complete the synthesis of amoproxan (27).⁹





Risocaine (28) manages to retain local anesthetic activity even without having a "basic ester" moiety.¹⁰ Its synthesis follows classic lines involving esterification of p-nitrobenzoic acid with thionyl chloride followed by reaction with propanol, and then catalytic reduction to complete the scheme.



Vasodilators may be of value in the treatment of conditions resulting from insufficient blood flow through tissues. One such agent incorporating a bisbasic ester moiety is prepared by reacting 3,4,5-trimethoxybenzoyl chloride with 3-chloropropanol to give 29, and condensing two molar equivalents of this with N,N'-dimethylethanediamine to give hexobendine (30).¹¹

c. Amides

As one would anticipate, the time honored Schotten-Baumann reaction and its variants are the key steps in putting this group of substances together. Their intrinsic interest to the medicinal chemist depends upon their pharmacological properties and, in some cases, preparation of some of the less common benzoic acid analogues.

Anticholinergic agents play a role in management of ulcers by decreasing the secretion of gastric acid
(36)

mediated by the neurohormone acetyl choline. *Proglumide* (*32*) is synthesized from the benzoyl amide of glutamic anhydride derivative *31* by reaction of the more activated carbonyl with dipropylamine.¹²



The diuretic clopamide (35) is synthesized from p-chlorobenzoic acid (33) by chlorosulfonation and subsequent ammonia treatment to give 34. This is converted to its acid chloride with thionyl chloride and reacted with the desired hydrazine derivative



(itself prepared by lithium aluminum hydride reduction of N-nitroso-2,6-dimethyl piperidine) in a Schotten-Baumann reaction to give *clopamide*.¹³ The related diuretics *diapamide* (36),¹⁴ *xipamide* (37),¹⁵

(37)

(38)

and *alipamide* $(38)^{16}$ are made by simple variants on this scheme.



The sedatives trimetozine (39), ¹⁷ and tricetamide (40), ¹⁸ the CNS stimulants ethamivan (41), ¹⁹ and sulpiride (42), ²⁰ the antihelmintic agents niclosamide (43), ²¹ clioxanide (44), ²² and bromoxanide (45), ²³ the coccidiostat alkomide (46), ²⁴ and the antiarrhythmic agent capobenic acid $(47)^{25}$ are all made from the corresponding benzoic acids in obvious ways.



2. DERIVATIVES OF ANILINE

The clinical success of hindered acetanilide derivatives, such as *lidocaine*, of course, resulted in the synthesis of many analogues. Branching in the acid moiety is consistent with activity as demonstrated by the local anesthetic properties of *etidocaine* $(48)^{26}$ and a formally cyclized analogue, *dexivacaine* (49).²⁷ *Etidocaine* is prepared from 2,6-dimethylaniline by sequential reactions with 2-bromobutyryl chloride and ethylpropylamine. The preparation of *dexivacaine* follows the same pattern. However, in this case, resolution by crystallization of its quinic acid salt was carried out, whereupon it was found that the Senantiomer was the longer acting.



Acetanilide is a well-established analgesic agent. It is perhaps not suprising then that butacetin (51) has such activity; however, it appears to have been synthesized while searching for antitubercular agents. The synthesis proceeds from 4-fluoronitrobenzene (50) <u>via</u> a nucleophilic aromatic displacement reaction with potassium <u>tert</u>-butoxide, followed by Raney nickel reduction and acetylation.²⁸ A molecular dissection of the alkaloid vasicine (52) ultimately resulted in the expectorant and mucolytic agent bromhexine (54).²⁹ The synthesis starts with displacement of halogen on 2-nitrobenzylbromide (53) by N-methyl cyclohexylamine, followed by Raney nickel and hydrazine reduction of the nitro group. Bromination in acetic acid then affords bromhexine.



Serotonin (55) is a putative neurotransmitter, especially in the central nervous system, and has a number of peripheral effects as well. There have been numerous attempts to associate disturbances in serotonin catabolism and anabolism with mental disease, and antagonists have been prepared as an aid to investigation of these theories and as potential therapeutic agents. BAS (56) is one such inhibitor and its structural similarity to 55 makes it understandable that it should be such. On the other hand, cinanserin (58) is 157 times more potent as a serotonin inhibitor than 56, and its structural relationship to either 55 or 56 is much less obvious. This underscores one of the more frustrating features of deliberate drug design--that the best analogues occasionally differ strikingly in structure from the lead molecule so that success requires an unsatisfying amount of semirandom molecular manipulation and a very close liason with the pharmacologist into whose hands the drugs are placed for evaluation. In any



event, *cinanserin* is synthesized from 2-aminothiobenzene (57) by S-alkylation using N,N-dimethyl-3chloropropylamine and NaOCH₃, followed by reaction with cinnamoyl chloride to give 58.³⁰



Phencarbamide $(60)^{31}$ is a structural analogue of acetylcholine which acts as an anticholinergic agent, possibly by serving as a false agonist. It is made by reacting N,N-diphenylcarbamoyl chloride (59) with 2-mercapto-N,N-diethylethamine.

Flubanilate (61) has central nervous stimulating activity and is synthesized conveniently from N-(2-dimethylamino)ethyl-3-trifluoromethylaniline by reaction with ethylchlorocarbonate.³²

A number of aminobenzophenone derivatives possess nonsteroidal antiinflammatory activity. Illustrative is *diflumidone* (63). Its synthesis involves treatment of 3-aminobenzophenone (62) with difluoromethanesulfonic anhydride in the presence of triethylamine.³³





(64)

The closely related antiinflammatory agent *triflumidate* (64) can be prepared by abstracting the now acidic NH proton of the trifluoromethyl analogue of 63 with sodium hydroxide and reacting the resulting anion with ethyl chlorocarbonate to give 64.³⁴

- 3. DERIVATIVES OF PHENOL
- a. Basic Ethers

The chemical fragment, OCCN=, occurs very frequently in drugs, perhaps deriving some inspiration from acetyl choline. The fact that drugs containing this unit do not possess some common pharmacological property suggests that the function is involved in transport rather than being a pharmacophore. Several agents containing this moiety are described in this section. *Boxidine (69)* has hypolipidemic properties.³⁵



It was synthesized from p-iodoanisole (65) by coppercatalyzed coupling with p-trifluoromethyliodobenzene (66) to give the expected statistical mixture from which unsymmetrical product 67 could be separated. Ether cleavage with HBr and HOAc gave 68; this was then alkylated with the aziridinium ion derived from N-(2-chloroethyl)pyrrolidine, using NaH as base, to complete the synthesis of *boxidine* (69).

The quaternary ammonium salt 73, thenium closylate, is an anthelmintic agent. Many substances of this general type are effective by interfering with nervous conduction, and thereby muscle tone, of intestinal worms. This allows their expulsion, not always in the dead state. The synthesis³⁶ proceeds from 2-thienylamine (70) by monoalkylation with 2phenoxyethyl bromide (71) to give secondary amine 72. This is converted by methyl iodide to the quaternary salt which is converted to the p-chlorobenzene sulfonate salt (73) for pharmacological purposes.



(<u>73</u>)

When 1,2-dichloropropane is reacted with o-benzylphenoxide ion (74), halide 75 results, which is then converted to the antitussive agent *benproperine* (76) on treatment with piperidine.³⁷



Guanethidine (77) was the first of a series of antihypertensive agents which act by interfering with adrenergic transmission. It was subsequently found that simple substitution of the guanidine function onto a nucleus with appropriate lipophilicity almost invariably affords such sympathetic inhibitors.



Thus, for example, guanidine analogues guanoxyfen (79) and guanochlor (82) also possess antihypertensive activity. Guanoxyfen is synthesized³⁸ by basecatalyzed condensation of phenol with chloroacetonitrile, followed by hydride reduction to amine 78. The guanido function is introduced by reaction with S-methylthiourea to give guanoxyfen (79). When 2-(2,6-dichlorophenoxy)ethyl bromide (80) is reacted with hydrazine to give 81, and this is reacted with S-methylthiourea, guanochlor (82) results.³⁹

b. Phenoxyacetic Acids

The clinical success of *clofibrate* has naturally led to the synthesis of numerous analogues intended for use as hypocholesterolemic agents. One of these, *clofenpyride* (84), is synthesized readily from pchlorophenoxy-2,2-dimethylacetic acid (83) by conversion to the acid chloride and reaction with 3-hydroxymethylpyridine.⁴⁰ Substitution of a single aromatic



ring in the place of the <u>gem</u>-dimethyl groups of 84 is compatible with activity. Interestingly, the resulting molecule, *halofenate* (90) is also reported to show uricosuric activity. Conversion of <u>p</u>-chlorophenylacetic acid (85) to its acid chloride (86) activates the benzylic methylene group to bromination with molecular bromine, and the resulting mixed dihalide (87) is reacted with methanol to give ester 88. Nucleophilic halide displacement with the sodium salt of m-trifluoromethylphenol gives intermediate 89, which is saponified with KOH, converted to the acid



chloride with thionyl chloride, and then esterified with N-acetylethanolamine to give halofenate (90).⁴¹

Insertion of a second aryl ether oxygen function is also consistent with hypocholesterolemic activity. Burger <u>et al</u>. have published an early and apparently general synthesis of such compounds.⁴² In the specific case of *lifibrate* (92), bis-(4-chlorophenoxy) acetic acid (91) is converted to the acid chloride with thionyl chloride, and then reacted with N-methyl piperidine-4-ol to give the desired basic ester 92.



A seemingly simple variation on these structures results in central stimulant activity instead. p-Methoxyphenyloxyacetic acid (93) is reacted with N,N-diethylethanolamine <u>via</u> the acid chloride to give mefexamide (94). 43



The diuretic properties of ethacrynic acid (95) were at one time attributed to its role as a Michael

acceptor. The enone was believed to react with SH groups on enzymes in the kidney. This interesting view was weakened by the discovery that some related molecules which do not possess this structural feature









still possess marked diuretic activity. An analogue of ethacrynic acid is synthesized by condensing 2,3dichloromethoxybenzene (96) with the acid chloride of thiophene α -carboxylic acid to give 97. Ether cleavage with AlCl₃, followed by sodium salt formation, etherification with ethyl chloroacetate, and then saponification gives ticrynafen (98).⁴⁴

Ethers of 1-Aminopropane-2,3-diol c. There has been enormous interest recently in the pharmacological properties of selective β -adrenergic blocking agents following the clinical success of propranolol. That the many pharmacological responses elicited by norepinephrine and epinephrine in various tissues are the consequence of macromolecular receptor substances of slightly different specificities has been known for some time. Such differences are often most conveniently demonstrated through use of selective inhibitors, and functional classifications of such receptors are usually made on that basis. Ahlquist devised a system of receptor classification based largely upon whether excitatory or inhibitory responses followed administration of adrenergic agents.45 The α -receptor was associated generally with excitatory responses (vasoconstriction, uterine and nictating membrane stimulation) while the β -receptor was associated with inhibitory responses (vasodilation, inhibition of uterine muscle).

While the physiological responses following β -receptor stimulation are many, those most prominent are those on the cardiovascular system and on the smooth muscles of the bronchial tree. Subsequently, a lack of faithful parallelism between the cardiac and bronchial effects led Lands <u>et al</u>.⁴⁶ to propose a further subdivision of the β -receptors into β_1 , which stimulates cardiac muscle and lipolysis, and β_2 , which relaxes bronchioles and influences the vasculature and shows metabolic effects. Epinephrine (99)

is an archetypal adrenergic agent stimulating α , β_1 , and β_2 receptors.



Some specific antagonists of interest in classifying receptors are tolazoline (100, α -receptor antagonist), dichloroisoproterenol (101, β -receptor antagonist), practolol (102, β_1 receptor antagonist), and bunitrolol (103, β_2 receptor antagonist). Recently described compound 103a departs from the previous structural norm and possesses strong β_2 receptor blocking selectivity. These classifications are rendered somewhat difficult because few of these agents are completely selective and may have additional pharmacological properties, such as varying degrees of intrinsic sympathomimetic agonist action. Isoproterenol (104) is an important agent for classification because of its selective β -receptor agonist activity. It is of special interest that its chronotropic (increase in heart rate) and inotropic (increase in force of contraction) effects exceed that of epinephrine; it is also used in the management of mild to moderate asthma due to its bronchodilating effect, resulting in increased vital capacity of the lungs.

It is in this context that propranolol (105) and its myriad analogues need to be judged. Administration of 105 leads to a decrease in heart rate, cardiac contractile force and myocardial oxygen consumption. These drugs often have some intrinsic adrenergic sympathomimetic activity which leads, i.a., to an increase in airway resistance of little consequence to most patients but of potential danger to asthmatics. Another factor of interest is a direct action on cell membranes, affecting their responsiveness to electrical stimulation and, in isolated atria, decreasing spontaneous frequency, maximal driving frequency, contractility and increasing the electrical threshold. In contrast to the β -blocking action, these "local anesthetic" actions are nonstereospecific. Whether these local anesthetic actions are important in antiarrhythmic action is being debated.

The therapeutic use of these agents is in control of cardiac arrhythmias, angina pectoris, and in essential and renovascular hypertension. The various ancillary activities lead to side effects and much effort has been expended to refine out these extraneous responses. It is not universally agreed whether some intrinsic sympathetic activity (I.S.A.) is desirable or not and, if so, how much a drug should have.



The means used to prepare these agents can be illustrated by the following examples. *Practolol* $(109)^{47}$ gives less clinical bronchoconstriction in some patients than propranolol because its receptor action is more selective. Serious occasional toxicity not related to β -blockade has led to its withdrawal from clinical use. A synthesis is available which relates the absolute configuration of the more potent

108

optical isomer to (+)-lactic acid. The glycerol derivative 106 is available from D-mannitol and retains the optical activity as the two primary alcohol functions are differentially protected. Displacement with sodium p-acetamidophenoxide gives 107 which is deblocked with dilute acid, selectively reacts at the primary alcohol function with one molar equivalent of tosyl chloride and pyridine, then treated with NaOH in dimethylsulfoxide to yield epoxide 108. Epoxide opening with isopropylamine leads to optically active practolol (109), showing that the l-compounds are related to R-(-)-epinephrine.

The synthesis of oxprenolol (111) follows a similar course.⁴⁹ Epoxide 110, readily synthesized by reaction of the sodium salt of pyrocatechol monoallylether with epichlorohydrin, is reacted either with isopropylamine or with HCl (to form the intermediate halohydrin) followed by isopropylamine.



Metoprolol (112), ⁵⁰ acebutolol (113), ⁵¹ atenolol (114), ⁵² and moprolol (115)²³ are all closely related

and made by this basic route or simple variations of it.



Replacement of isopropylamine by <u>tert</u>-butyl amino often results in an increase in potency. This substitution is used in the β -blockers *bunitrolol* (116), ⁵⁴ *bufuralol* (117), ⁵⁵ *bunolol* (118), ⁵⁶ *nadolol* (119), ⁵⁷ and *phenbutalol* (120). ⁵⁸ *Tazolol* (121)⁵⁹ whose structure is similar, is not a good β -blocker, possessing substantial ISA.

Substitution of groups other than <u>i</u>-propyl or <u>t</u>-butyl on nitrogen also leads to active compounds. Primary amine 122 is reacted with p-(β -chloroethoxy)benzamide (123) to give the β -blocker, tolamolol (124).⁶⁰



- 4. ARYLSULFONES AND SULFONAMIDES
- a. Sulfones

Until the development of the antibacterial sulfones, Hanson's Disease (leprosy) remained a potentially horrible affliction, treated with largely ineffective ancient remedies. The antibacterial sulfonamides do not do well against this disease and, interestingly, the sulfones which are effective, are not very useful



(125)





against most other bacterial infections. Dapsone (125) is such an agent. It is somewhat inconvenient to administer to patients because of its rather low water solubility. In the search for more easily administered drugs, 125 was reacted with bromoacetic acid to give acediasulfone (126) which can be administered as a water soluble salt.⁶¹

Acedapsone (127), which is conveniently prepared by acetylation of dapsone, was intended to be a prodrug.⁶² Leprous patients being treated with dapsone were observed to have a lower incidence of malaria and acedapsone was made to capitalize on this observation. It, indeed, has both antileprotic and antimalarial activity.

b. Sulfonamides

Because of bacterial resistance and unacceptable side effects in some patients, the antibacterial sulfonamides no longer enjoy the clinical vogue they once had. Still, their cheapness, undeniable efficacy in susceptible infections, and the hope of overcoming their deficiencies leads to a continuing interest despite thousands having been synthesized to date. Some of the more significant agents not included in Volume I of this work follow.

Generally, N_1 -acylsulfonamides are less effective than those having a single N_1 -aryl group. One such acyl analogue, sulfabenzamide (130) is prepared simply from sulfanilamide (128) by bisbenzamide formation (to 129) using benzoyl chloride and pyridine, followed by partial saponification.⁶³

112



The classic syntheses of the antibacterial sulfonamides involve reaction of the appropriate arylamine with an acid addition salt of p-aminobenzenesulfonyl chloride, or p-nitrobenzenesulfonyl chloride followed by reduction. Chemical interest largely resides in preparation of the corresponding arylamines. For the synthesis of *sulfacytine* (134), N-ethyl uracil (131) was converted to its thioamide (132) by reaction with phosphorous pentasulfide. The newly introduced sulfur is then displaced with ammonia in methanol to give 133. Standard reactions complete



the synthesis of 134.⁶⁴ Reaction of cyanoacetone (135) with phenylhydrazine gives the corresponding pyrazole (136), which is then converted to sulfazamet (137) in the usual way.⁶⁵ An antibacterial agent promoted for use in ulcerative colitis is made by diazotization of sulfapyridine (138) and coupling of the diazonium salt (139) with salicylic acid to give sulfasalazine (140). 66



Mafenide (142) was synthesized in part to see whether the p-amino group of the classical sulfonamides had to be attached directly to the ring for efficacy as an antibacterial agent. The answer is apparently yes.⁶⁷ Reduction of p-cyanobenzenesulfonamide (141) produces mafenide, which is not a clinically useful antibacterial agent.





 $(\underline{141})$ R = CN $(\underline{142})$ R = CH₂NH₂

Coccidiosis is an economically significant respiratory disease of fowl. During the course of studies directed toward antimalarial agents, *sulfanitran (143)* was prepared and found to be a coccidiostat. It is prepared conveniently by reaction of p-acetoamidobenzenesulfonyl chloride with p-nitroaniline in acetic acid.⁶⁸



(143)



Benzenesulfonamides having two substituents on N_1 usually have poor antibacterial potency. Such is the case with *azabon* (146). This central stimulant is prepared in the usual fashion from 3-azabicyclo-[2.2.2]nonane (145), which is itself prepared by pyrolysis of aliphatic diamine 144.⁶⁹



Ambuside (149), a diuretic, is prepared from cyclic urea derivative 147 by allylation of the more acidic NH group with allyl bromide by means of NaH, followed by hydrolytic ring opening to give 2-allylsulfamyl-5-chloro-4-sulfamylaniline (148). This is in turn treated in acid with 2-ketopropionaldehyde dimethylacetal to give the Schiff base ambuside (149). ⁷⁰ The enolanil form (150) of ambuside shows some similarity to the open form of some of the cyclic thiazide diuretics (151) which have been speculated to be the active form of these molecules.

c. Sulfonylureas Linear descendants of the antimicrobial sulfonamides, the orally active sulfonylureas continue to be of interest as alternatives to insulin injections in patients with adult-onset diabetes. *Tolpyrramide* (153) is synthesized from unsymmetrical O-methylurea derivative 152 and tosyl chloride, followed by mild acid treatment to cleave the 0-methyl group. 71



Glyparamide (155) is made by displacement of the best leaving group of unsymmetrical urea 154 with sodio p-chlorobenzenesulfonamide.⁷² *Glibornuride* (159) is an endo-endo derivative made from camphor-



3-carboxamide (156) by borohydride reduction (<u>exo</u> approach) (to 157), followed by a Hoffman reaction to carbamate 158, followed by displacement with sodiotosylamide to give glibornuride.⁷³ Glyoctamide (160) is the tosylamide of cyclooctylurea.⁷⁴ Glipizide (163) is synthesized from 5-methylpyrazine-2-carboxylic acid (161) and 4-(2-aminoethyl)benzene sulfonamide to give sulfonamide 162, which forms glipizide (163) on reaction with cyclohexylisocyanate and base in acetone.⁷⁵









(<u>158</u>)









118

Though *glymidine* (*164*) does not contain a sulfonylurea moiety, this function is probably fulfilled by the aminopyrimidine nucleus, which can be considered to be the cyclized equivalent. It is formed simply by reaction of the corresponding alkoxyaminopyrimidine with benzene sulfonyl chloride.⁷⁶

5. FUNCTIONALIZED BENZENE DERIVATIVES

a. Alkyl Analogues

Parkinson's Disease has been fairly convincingly demonstrated to be the manifestation of a deficit of brain dopamine. Administration of this biogenic amine is ineffective in alleviating the symptoms of this disease since the drug fails to cross the blood-brain barrier. Some success has been achieved by administering the amino acid precursor of dopamine: dihydroxyphenylalanine (DOPA). Though this last substance does penetrate the brain, its activity is limited by prior degradation-starting with decarboxylation in the periphery. A compound which would inhibit the enzyme which catalyzes this first step, DOPA decarboxylase, should permit more efficient utilization of DOPA. A compound very closely related structurally to the substrate for the enzyme fulfills this function. Carbidopa 168 was designed for this purpose. Carbidopa's synthesis begins with a modified Strecker reaction using hydrazine and potassium cyanide on arylacetone 165 to give 166. This is then hydrolyzed with cold HCl to give carboxamide 167.



More vigorous hydrolysis with 48% HBr cleaves the amide bond and the arylether group to produce *carbidopa* (168).⁷⁷ There is some evidence that *carbidopa* has some anti-Parkinsonian activity in its own right. If this is confirmed, then its mode of action will be different from that for which the drug was designed and prepared.

Another aminoacid-like drug is the antineoplastic agent melphalan (173). Tumor cells spend less time in resting phases than normal cells so at any given time, they are more likely to be metabolically active than most normal host cells. The rationale behind incorporating an alkylating function in a molecule resembling a primary cellular metabolite was to get a greater safety margin by fooling tumor cells into taking up the toxin preferentially. p-Nitrophenylalanine (169) was converted to its phthalimide analogue by heating with phthalic anhydride, and this was converted to its ethyl ester (170). Catalytic reduction produced the aniline (171). Heating in acid with ethylene oxide led to 172, which was converted to the bischloride with phosphorous oxychloride, and the protecting groups were removed by heating in hydrochloric acid to give melphalan (173).⁷⁸



Baclofen (176), a muscle relaxant and hypnotic, is synthesized from ethyl p-chlorocinnamate (174) <u>via</u> the Triton B catalyzed Michael addition of nitromethane (to 175) followed by Raney nickel reduction and saponification. Baclofen is formally a GABA (gamma-aminobutyric acid) analogue.⁷⁹



Reaction of p-chlorobenzylmagnesium chloride with the Mannich product from 2-butanone (177) produces the antitussive agent, *clobutinol* (178).⁸⁰ The tranquilizer *cintriamide* (179) is prepared most conveniently by a simple Shotten-Baumann reaction of the acid chloride.⁸¹ For reasons that are not very clear, the 1,2,3-trimethoxybenzene moiety is frequently associated with CNS activity.



Very reactive nitrogen mustards and aziridinecontaining molecules are usually too toxic for general therapeutic use, but find use in neoplastic disease. Benzodepa (182) is such an agent. Treatment of ethyl carbamate with phosphorous pentachloride leads to cyanate 180 which readily adds benzyl alcohol to produce carbamate 181. Displacement of the active



chlorines with ethyleneimine leads to the very reactive benzodepa (182).⁸² It was previously known that carbamates and bisaziridininylphosphinyl agents had antitumor properties, so it was natural to combine both moieties in a single molecule to see if synergism would develop.

122

As noted above, guanido-containing drugs often exhibit antihypertensive activity. Interposition of an additional nitrogen atom is consistent with activity. There is some evidence to suggest that these hydrazines owe their activity to a mechanism different from the guanidines. One such derivative was originally synthesized to be a herbicide.⁸³ Hydrazone formation



between 2,6-dichlorobenzaldehyde and hydrazinyl guanidine 183 leads efficiently to guanabenz (184). The closely related analogue guanoxabenz (185) is prepared in the analogous fashion using the hydrazinyloxyguanidine derivative prepared by reacting thiomethylimine 186 with hydroxylamine and then with 2,6dichlorobenzaldehyde.⁸⁴

A group of arylalkylketones containing a basic substituent in the side chain shows CNS activities. *Roletamide* (190) is a hypnotic agent. It is prepared from 3,4,5-trimethoxybenzaldehyde (187) by addition of sodium acetylide (to give 188), followed by Jones oxidation of ethynylarylketone 189. Michael addition of pyrrolidine-3-ene leads to *roletamide* (190).⁸⁵



Reaction of m-chlorobenzonitrile with ethyl Grignard reagent produces ethylarylketone 191. Bromination in methylene chloride followed by displacement of the α -bromoketone moiety with <u>t</u>-butylamine leads to the antidepressant agent *bupropion* (192).⁸⁶ While the closely related central stimulant *pyrovalerone* (193) can also be made simply by reacting the requisite α -haloaralkylketone with pyrrolidine, a



more interesting synthesis goes through quaternary amine 194 which undergoes a Stevens rearrangement on treatment with base to provide intermediate 195, which is hydrogenated to pyrovalerone.⁸⁷ This mechanistic interpretation is supported by studies with unsymmetrical olefins wherein it is seen that the double bond migrates on conversion of 194 to 195.



Conversion of a ketone to a highly substituted imine interestingly leads to a compound which shows analgesic activity, *anidoxime (197)*. Phenyl 2-diethylaminoethyl ketone is converted to its oxime (196) in the usual way, and this is converted to *anidoxime* by reaction with p-methoxyphenylisocyanate.⁸⁸



An arylamidine found subsequently to have antiarrythmic activity was actually synthesized in the hope of producing a hypoglycemic agent. Iminochloride 198 is prepared from the corresponding benzamide and the chlorine is displaced with n-amylpiperidine to produce *bucainide* (199).⁸⁹ To posit a similarity to



the well-established antiarrythmic benzamide procainamide and its congeners is perhaps not too fanciful.

While some arylaliphatic acids are established as antiinflammatory agents, it is interesting to note that some arylketones share this activity. *Fenbufen* (200) is prepared simply by a Friedel-Crafts acylation of biphenyl with succinic anhydride.⁹⁰ The same reaction using cyclohexylbenzene leads to 201.



Chlorination enhances activity and is accomplished by treatment of 201 with chlorine in methylene chloride catalyzed by aluminum chloride. The nonsteroidal antiinflammatory agent *bucloxic acid* (202) results.⁹¹

b. Miscellaneous Derivatives

Reaction of 2,6-ditertiarybutyl-4-thiolphenol with acetone leads to the dithioketal *probucol (203)* which has hypolipidemic activity.⁹²



126

Some tumors are estrogen-dependent and the use of an antiestrogen has therapeutic value. One such antineoplastic agent appears to be patterned after *clomiphene*. Complex aryl ketone 204 is treated with phenyl magnesium chloride and the resulting tertiary



carbinol is dehydrated. The resulting isomers are separated to give *tamoxifen* (205). Structural assignment amongst the isomers is performed by pmr measurements.⁹³

REFERENCES

- W. Ruyle, L. H. Sarett and A. Matzuk, French Patent 1,522,570 (1968); Chem. Abstr., 71: P30241u (1969).
- W. Ruyle, L. H. Sarett and A. Matzuk, South African Patent 67 01,021 (1968); Chem. Abstr., 70: P106,209k (1969).
- 3. P. W. Fect, J. Med. Chem., 14, 432 (1971).
- G. F. Holland, German Patent 2,145,686 (1972); Chem. Abstr., 77: P48046m (1972).

- 5. P. F. Juby, T. W. Huidyma and M. Brown, J. Med. Chem., 11, 111 (1968).
- G. B. Fregnan, A. Subissi and A. L. Torsello, *I1 Farmaco, Ed. Sci.*, 30, 353 (1975); A. Salimbeni,
 E. Manghisi and M. J. Magistretti, *I1 Farmaco, Ed. Sci.*, 30, 276 (1975).
- 7. S. A. Friere, U. S. Patent 2,604,488 (1952): Chem. Abstr., 48: 12,807d (1954).
- C. Cavallito and J. S. Buck, J. Am. Chem. Soc., 65, 2140 (1943).
- 9. R. Y. Mauvernay, N. Busch, J. Simond and J. Moleyre, U. S. Patent 3,781,432 (1970); Chem. Abstr., 74: 141,861w (1971).
- J. Buchit, K. H. Hetterich and X. Pereira, Arzneimittel forschung, 18, 1 (1968).
- 11. O. Kraupp and K. Schloegl, Austrian Patent 231,432 (1964); Chem. Abstr., 60: 15786g (1964).
- 12. Anonymous, Netherlands Patent 6,510,006 (1966); Chem. Abstr., 65: 3793b (1966).
- E. Jucker and A. Lindenmann, Helv. Chem. Acta, 45, 2316 (1962).
- 14. M. L. Hoefle, German Patent 1,158,927 (1963); Chem. Abstr., 60: 10,608a (1964).
- 15. Anonymous, Netherlands Patent 6,607,680 (1966); Chem. Abstr., 67: 21,706h (1967).
- 16. H. A. DeWald and M. L. Hoefle, U. S. Patent 3,043,874 (1962); Chem. Abstr., 57: 16,503h (1962).
- G. R. Pettit, M. F. Baumann and K. H. Rangammal, J. Med. Chem., 5, 800 (1962).
- M. E. Kuehne and B. F. Lambert, J. Am. Chem. Soc., 81, 4278 (1959).
- K. Kratzl and E. Krasnicka, Monatsh. Chemie, 83, 18 (1952).
- 20. Anonymous, Netherlands Patent 6,500,326 (1965); Chem. Abstr., 64: 3,486h (1966).
- B. Duhm, W. Maul, H. Medenwald, K. Patzschke and L. A. Wagner, Z. Naturwissenschaften, 16b, 509 (1961).
- 22. Anonymous, Netherlands Patent 6,604,303 (1966); Chem. Abstr., 66: 55,247d (1967).
- 23. W. H. Meek, German Patent 2,347,615 (1975); Chem. Abstr., 83: 58,480m (1975).
- 24. D. B. Cosulich, D. R. Seeger, M. J. Fahrenbach,
 K. H. Collins, B. Roth, M. E. Hultquist and J.
 M. Smith, Jr., J. Am. Chem. Soc., 75, 4675 (1953).
- A. Garzia, German Patent 2,034,192 (1971); Chem. Abstr., 75: 5513c (1971).
- 26. H. J. F. Adams, G. H. Kronberg and B. H. Takman, German Patent 2,162,744 (1972); Chem. Abstr., 77: 101,244c (1972).
- 27. B. F. Tullar, Acta Chem. Scand., 11, 1183 (1957); J. Med. Chem., 14, 891 (1971); Acta Pharm. Sueica, 8, 361 (1971).
- 28. K. Bowden and P. N. Green, J. Chem. Soc., 1795 (1954).
- 29. J. Keck, Ann., 662, 171 (1963).
- 30. J. Krapcho, B. Rubin, A. M. Drungis, E. R. Spitzmiller, C. F. Turk, J. Williams, B. N. Craver and J. Fried, J. Med. Chem., 6, 219

(1963).

- 31. A. Laurent and J. Vilmer, Ann. Pharm. Fr., 29, 569 (1971).
- 32. Anon., Netherlands Patent 6,405,529 (1964); Chem. Abstr., 62: 10,368g (1965).
- 33. J. K. Harrington and J. E. Robertson, German Patent 1,917,821 (1969); Chem. Abstr., 73: 14,477e (1970).
- 34. J. K. Harrington, J. E. Robertson, D. C. Kvain, R. R. Hamilton, K. T. McGurran, R. J. Trancik, K. F. Swingle, G. G. I. Moore and J. F. Gerster, J. Med. Chem., 13, 137 (1970).
- 35. Anon., Netherlands Patent 6,516,582 (1966); Chem. Abstr., 65: 16,901f (1966).
- 36. F. C. Copp, British Patent 864,885 (1961); Chem. Abstr., 55: 24,792a (1961).
- 37. Anon., British Patent 914,008 (1962); Chem. Abstr., 58: 12,523a (1963).
- 38. D. I. Barron, P. M. G. Bavin, G. J. Durant, I. L. Natoff, R. G. W. Spickett and D. K. Vallance, J. Med. Chem., 6, 705 (1963).
- 39. G. J. Durant, G. M. Smith, R. G. W. Spickett and S. H. B. Wright, J. Med. Chem., 9, 22 (1966); Anon., Belgian Patent 629,613 (1963); Chem. Abstr., 60: 14,437d (1964).
- 40. Anon., Netherlands Patent 6,610,738 (1968); Chem. Abstr., 68: 39,487t (1968).
- 41. W. A. Bulhofer, South African Patent 67 05,870 (1967); Chem. Abstr., 71: 101,563g (1969).
- 42. A. Burger, D. G. Markees, W. R. Nes and W. L. Yost, J. Am. Chem. Soc., 71, 3307 (1949).

- 43. G. Thuillier, P. Rumpf and B. Saville, Bull. Soc. Chim. Fr., 1786 (1960).
- 44. J. J. Godfroid and J. E. Thuillier, German Patent 2,048,372 (1971); Chem. Abstr., 75: 93,435s (1971).
- 45. R. P. Ahlquist, Am. J. Physiol., 153, 586 (1948).
- 46. A. M. Lands, A. Arnold, J. P. McAuliff, F. P. Luduena and T. G. Brown, Jr., Nature, 214, 597 (1967).
- 46a. G. Leclerc, A. Mann, C. Wermuth, N. Bieth and J. Schwartz, J. Med. Chem., 20, 1657 (1977).
- 47. J. C. Danilewicz and J. E. G. Kemp, J. Med. Chem., 16, 168 (1973).
- 48. M. Dukes and L. H. Smith, J. Med. Chem., 14, 326 (1971).
- 49. Anon., Belgian Patent 669,402 (1966); Chem. Abstr., 65: 5402d (1966).
- 50. A. E. Brandstrom, P. A. E. Carlsson, S. A. I. Carlsson, H. R. Corrodi, L. Ek and B. A. H. Ablad, German Patent 2,106,209 (1971); Chem. Abstr., 76: 10,427c (1972).
- 51. K. R. H. Wooldridge and B. Berkeley, South African Patent 68 08,345 (1969); Chem. Abstr., 72: 78724v (1970).
- 52. A. M. Barrett, R. Hull, D. J. LeCount, C. J. Squire and J. Carter, German Patent 2,007,751 (1970); Chem. Abstr., 73: 120,318p (1970).
- 53. G. Crocl, Arzneimittelforsch., 20, 1074 (1970).
- 54. H. Koeppe, K. Zeile and A. Engelhardt, South African Patent 68 03,783 (1968); Chem. Abstr., 71: 21,878y (1969).

- 55. Anon., Netherlands Patent 6,606,441 (1966); Chem. Abstr., 67: 21,808t (1967).
- 56. E. J. Merrill, J. Pharm. Sci., 60, 1589 (1971).
- 57. F. P. Hauck, C. M. Cimarusti and V. L. Narayanan, German Patent 2,258,995 (1973); Chem. Abstr., 79: 53,096y (1973).
- 58. H. Ruschig, K. Schmitt, H. Lessenich and G. Haertfelder, South African Patent 68 07,915 (1969); Chem. Abstr., 72: 90,054j (1970).
- 59. J. A. Edwards, B. Berkoz, G. S. Lewis, O. Helpern, J. H. Fried, A. M. Strosberg, L. M. Miller, S. Urich, F. Liu and A. P. Roszkowski, J. Med. Chem., 17, 200 (1974).
- J. Augstein, D. A. Cox, A. L. Ham, P. R. Leeming and M. Snarey, J. Med. Chem., 16, 1245 (1973).
- 61. E. L. Jackson, J. Am. Chem. Soc., 70, 680 (1948).
- 62. E. F. Elslager, Z. B. Gavrilis, A. A. Phillips and D. F. Worth, J. Med. Chem., 12, 357 (1969).
- 63. C. Siebenmann and R. J. Schnitzer, J. Am. Chem. Soc., 65, 2126 (1943).
- 64. L. Doub, U. Krolls, J. M. Vandenbelt and M. W. Fisher, J. Med. Chem., 13, 242 (1970).
- 65. G. B. Crippa and M. Guarnari, Gazz. Chim. Ital., 85, 199 (1955): J. Seydel and E. Kruger-Thiemer, Arzneimittelforsch., 14, 1294 (1964).
- 66. A. Korkuczanski, Prezemsyl Chem., 37, 162 (1958).
- 67. E. Muller, J. M. Sprague, L. W. Kissinger and L.
 F. McBurney, J. Am. Chem. Soc., 62, 2099 (1940).
- 68. R. G. Shepherd, J. Org. Chem., 12, 275 (1947).
- 69. A. W. Pircio and C. S. Krementz, U. S. Patent

3,351,528 (1967); Chem. Abstr., 68: P38,496v (1968).

- 70. J. E. Robertson, D. A. Dusterhoft and T. F. Mitchell, Jr., J. Med. Chem., 8, 90 (1965).
- 71. E. Walton, British Patent 872,102 (1961); Chem. Abstr., 57: P785g (1962).
- 72. G. F. Holland and W. M. McLamore, U. S. Patent 3,033,902 (1962); Chem. Abstr., 57: Pll,109f (1962).
- 73. K. Hohenlohe-Oehringen, Monatsh. Chem., 101, 610 (1970); H. Breitschnider, K. Hohenlohe-Oehringen and K. Grassmeyr, ibid., 100, 2133 (1969).
- 74. Anon., French Patent 1,558,886 (1969); Chem. Abstr., 72: P43,231e (1970).
- 75. V. B. Ambrogi and W. Logemann, German Patent 2,012,138 (1970); Chem. Abstr., 73: 120,674b (1970).
- 76. K. Gutsche, A. Harwart, H. Horstmann, H. Priewe,
 G. Raspe, E. Schraufstatter, S. Wirtz and U.
 Worfel, Arzneimittelforsch., 14, 373 (1964).
- 77. M. Sletzinger, J. M. Chemerda and F. W. Bollinger, J. Med. Chem., 6, 101 (1963).
- 78. F. Bergel, V. C. E. Burnop and J. A. Stock, J. Chem. Soc., 1223 (1955); F. A. Bergel and J. A. Stock, *ibid.*, 2409 (1954).
- 79. F. Uchimaru, M. Sato, E. Kosasayama, M. Shimizu and H. Takashi, Japanese Patent 70 16,692 (1970); Chem. Abstr., 73: 77,617w (1970).
- 80. Anon., British Patent 898,010 (1962); Chem. Abstr., 57: 12381i (1962).

- 81. R. B. Moffett, J. Med. Chem., 7, 319 (1964).
- Z. B. Papanastassiou and T. J. Bardos, J. Med. Chem., 5, 1000 (1962).
- 83. J. Yates and E. Haddock, British Patent 1,019,120 (1964); Chem. Abstr., 64: PC11132h (1966).
- 84. W. J. Houlihan and R. E. Manning, German Patent 1,902,449 (1969); Chem. Abstr., 71: Pl23963q (1969).
- 85. S. Safir and R. P. Williams, Belgian Patent 670,495 (1966); Chem. Abstr., 65: PC13615c (1966).
- 86. D. A. Yeowell, German Patent 2,064,934 (1971); Chem. Abstr., 76: P33965r (1972).
- 87. W. Heffe, Helv. Chim. Acta, 47, 1289 (1964).
- 88. M. J. Karten and M. L. Kantor, German Patent 1,805,716 (1969); Chem. Abstr., 71: 980916g (1969).
- 89. J. R. Shroff and V. Bandurco, U. S. Patent 3,793,322 (1974); Chem. Abstr., 80: P96018n (1974).
- 90. A. S. Tomcufcic, R. G. Child and A. E. Sloboda, German Patent 2,147,111 (1972); Chem. Abstr., 76: P158368e (1972).
- 91. F. Krausz, H. Demarne, J. Vaillant, M. Brunaud and J. Navarro, Arzneimittelforsch., 24, 1360 (1974).
- 92. M. B. Neuworth, R. J. Laufer, J. W. Barnhart, J. A. Sefranka and D. D. McIntosh, J. Med. Chem., 13, 722 (1970).
- 93. D. J. Collins, J. J. Hobbs and C. W. Emmens, J. Med. Chem., 14, 952 (1971).

134

Early interest in steroid chemistry centered about cholesterol, the bile acids, and the cardiotonic glycosides, but a dramatic expansion took place in the 1930s with the discovery of steroidal sex hormones and the adrenal cortical hormones. As each of the major steroid structures was elucidated, efforts were bent toward developing synthetic methods for their preparation. The impetus for this work was variously to provide amounts of compound sufficient for more detailed pharmacology and clinical application, to prepare orally active analogues, to prepare substances of intrinsic non-hormonal pharmacological activity, and, in some cases, to provide compounds that would antagonize the action of endogenous hormones.

The large number of entries outlined in this chapter might mislead the casual reader into assuming that these represent a correspondingly large number

of drugs in actual clinical use. This is in fact not the majority of commercial steroid drugs are to so: be found in the first volume of this work. The medicinal chemistry and pharmacology of synthetic steroids was a field of intensive concentration for the better part of two decades; numerous compounds were thus produced which showed enough clinical promise to be assigned a generic name, but for one reason or another, most failed to find a place on the drugstore shelf. The fact that so many of these compounds do have generic names indicates that they have interesting activity in various animal assays, and have shown sufficient clinical promise to merit inclusion in this work.

The numbering system and normal stereochemistry of the steroids of interest to this chapter are as follows:



This stereochemical pattern is taken for granted in the following structures with only departures being detailed.

1. ESTRANES

The prototype for the estrane series is the female sex hormone estradio1 (1). Estrogens have important

136

applications as replacement therapy for hormonedeficient states found in menopausal and postmenopausal women for the treatment of menstrual irregularities, failure of ovarian development, and in treatment of prostatic carcinoma, etc. These compounds also constitute an essential ingredient for the oral contraceptives. It is important to recall that when the synthetic work was done, the Pill was as yet untainted by any shadow and was regarded as an unmitigated boon. There seemed, in fact, to be good reasons for developing new estrogens of greater potency and specificity. It is only fairly recently that there have been serious guestions raised about the safety of long-term treatment with exogenous estrogenic compounds, resulting in a lessening commercial interest in these agents.



Reaction of estrone (2) with an excess of the lithium reagent from 3-iodofuran gives intermediate diol 3. The stereochemical assignment follows from the well-known propensity of steroids for attack from the less-hindered backside (α) of the molecule. Acylation of 3 with acetic anhydride then affords the estrogen estrofurate (4).¹

137

One of the routes for metabolism of the natural estrogens involves oxidation at the 16-position. The resulting compounds (estriols) show paradoxical endocrine activities in animal models. Thus, although these metabolites show estrogenic activity in their own right, they can to some extent block the action of concurrently administered estradiol. The unnatural estriol analogue epimestrol (8) shows this kind of activity.

One of the routes to epimestrol begins with acylation of estradiol with benzoyl chloride to give the dibenzoate 5. Pyrolysis of the ester leads to formation of the 16,17-olefin. Hydroxylation by means of osmium tetroxide affords the cis-diol 7 due to the intermediacy of the cyclic osmate ester (6a); attack of the reagents from the α side insures formation of the 16,17 α -diol.² Saponification is followed by alkylation of the phenolic hydroxyl group with dimethyl sulfate in the presence of base to afford epimestrol (8).³



Replacement of a ring carbon by a heteroatom, such as nitrogen, has proven a fruitful modification in many classes of medicinal agents. The resulting analogues often possess the same qualitative activity as the parent compound. Although this strategy has been applied extensively to the steroids. it has not met with overwhelming success. Two cases of substitution by N in which interesting activity was obtained both contain the heteroatom at the 8-position. Such derivatives are most conveniently prepared by total synthesis. For example, condensation of the substituted phenethylamine 9 with 2-cyclopentanonepropionic acid (10) affords directly the bicyclic lactam 12, as a mixture of isomeric eneamides. Though the precise order of the steps is not clear, the reaction can be rationalized as proceeding via enamine 11; enamide formation will then give the observed products. Catalvtic reduction affords the lactam with the expected cis ring junction (13). Cyclization by means of phosphorus oxychloride then gives the tetracyclic quaternary salt (14). Treatment with hydrobromic acid serves both to cleave the methyl ether and to replace the counterion by bromide. There is thus obtained guinodinium bromide (15). 4 This compound interestingly exhibits antiarrhythmic rather than hormonal activity, possibly in part because of lack of D-ring functionality required for estrogen receptor activation.



The scheme used to prepare the direct 8-azaanalogue 21 of estrone bears at least formal similarity to the Torgov-Smith steroid total synthesis sequence. Acylation of the phenethylamine 9 with acryloyl chloride gives amide 16. Michael addition of dimethylamine followed by Bischler-Napieralski cyclodehydration gives the dihydroisoquinoline, 17. Reaction of the heterocycle with 2-methylcyclopentanel,3-dione in the presence of pyridine leads directly to tetracyclic intermediate 20.⁵ The first step in this transformation probably consists in formation of the olefin 18 by elimination of dimethylamine. Michael addition of the anion from the cyclopentanedione gives a transient intermediate such as 19. Reaction of the enamine nitrogen with one of the carbonyl groups leads to the corresponding cyclized dieneamine 20. Catalytic reduction leads to stereoselective introduction of hydrogen at both C-9 and









C-14 from the α face. It should be noted that except for the methyl group at C-13, 20 is quite flat; it is not unreasonable to assume that adsorption to the catalyst will take place at the face opposite that substituent, thus leading to the observed stereochemistry. The product is, of course, racemic. Reaction of 20 with lithium acetylide completes the synthesis of estrazinol (22).⁶ It is of note that, in contrast to 15, this compound shows activity as an estrogen.

Reduction of the aromatic A ring of the estratrienes and appropriate substitution at the 17-position leads to compounds that show either androgenic or progestational activity. These 19-nor steroids tend to have much better oral activity than their 19-methylated counterparts. Orally active androgens have found some use both in replacement therapy for androgen deficiency and as agents which will reverse protein loss in various pathological wasting diseases (as anabolic agents). Some controversial use is also found in increasing the body mass of professional athletes. By far the largest clinical application for the orally active progestins is as a component part of oral contraceptives.

Reduction of 19-nortestosterone $(23)^7$ with sodium borohydride leads to a mixture of isomers consisting largely of the 3 β -alcohol (24); the lack of stereospecificity can be traced back to the relative remoteness of that 3-position from chiral centers which could direct the incoming reagent. Acylation of diol 24 with acetic anhydride in the presence of sodium acetate affords the anabolic agent bolandiol diacetate (25).⁸



A fairly common strategy for converting a drug to an agent which is excreted more slowly and may be longer acting pharmacologically consists of the preparation of a very lipophilic derivative. This is then administered by subcutaneous or intramuscular injection in an oil solution. The drug or its hydrolysis product then slowly leaches out of that oily depot to provide long-lasting levels in the blood. Reaction of 19-nortestosterone with adamantoyl chloride affords the longacting anabolic agent *bolmantalate* (26).⁹ There is some evidence to suggest that this ester is not a prodrug, but has hormonal activity in its own right.

The presence of a 7α -methyl group has been found to potentiate anabolic activity. Acetylation of 19nortestosterone affords the corresponding 17-acetate

(27).Treatment of this compound with chloranil results in dehydrogenation at C-6,7 and thus formation of the 4,6-diene-3-one moiety. Reaction of 28 with methyl Grignard reagent in the presence of cuprous bromide leads to conjugate (1,6) addition from the bottom face of the molecule with concomitant loss of the ester function from C-17 to give the 7α -methyl derivative (29). Oxidation of the alcohol at C-17 then affords diketone 30. Condensation of that product with pyrrolidine leads, because of the highly hindered nature of the ketone at C-17, to selective formation of the 3-enamine (31). Addition of methylmagnesium bromide followed by hydrolysis of the enamine function gives mibolerone (32).¹⁰ This last has, interestingly, recently been introduced as a canine oral contraceptive.



The formal replacement of the methyl group at C-17 by ethynyl leads, in the 19-nor series, from compounds which show androgenic activity to agents active The prototype for this series, and in as progestins. fact the compound used most widely in oral contraceptives, is norethindrone (33). It is of note that the analogue missing the ketone at C-3 retains this activity. Condensation of ethane dithiol with 19nor-testosterone affords the corresponding thicketal (34). Desulfurization with sodium in liquid ammonia affords 35. Oxidation affords the 17-ketone: reaction with lithium acetylide gives the progestin *cingestol* (37), ¹¹ A similar scheme on the isomeric deconjugated ketone 38 (obtained by hydrolyzing the enol ether product from the Birch reduction of estradiol methyl ether under mild conditions) gives tigestol (39).¹²



An unusual variation on this theme involves a compound containing both extended conjugation involving the bond connecting rings AC and a haloacetylene Reaction of ketone 40^{13} with the anion moietv. obtained by treatment of *cis* 1,2-dichloroethylene with methyl lithium affords chloroacetylene 41. This reagent can be generated either by formation of the organometallic agent by abstraction of a proton followed by loss of hydrogen chloride from the adduct or, more likely, by elimination of HCl from the ethylene followed by formation of the lithium reagent from the resulting acetylene. Hydrolysis of the enol ether under mild conditions (acetic acid) affords the unconjugated ketone 42. Treatment of that compound in pyridine with bromine leads to the potent oral progestin ethynerone (44).¹⁴ This last reaction can be rationalized by assuming that the first step consists of addition of bromine to the double bond at C-5,10 (43); double dehydrohalogenation will give the observed product. It is interesting to observe that 44 does not enolize to give an aromatic A ring.



146

The potentiation observed in the 19-nor androgens by inclusion of a C-7 methyl group is observed even in the presence of the 17-ethynyl function. Dehydrogenation of testosterone propionate (45) by means of chloranil gives the corresponding 4,6-diene (46). Conjugate addition of methyl magnesium bromide leads to the 7α -methyl derivative 47 along with the 7β epimer. Treatment of the major product with DDQ leads in this case to the cross-conjugated 1,4-diene. It is likely that the direction of this second dehydrogenation is mandated by the presence of the methyl group at C-7; this group may hinder the approach of reagent to the center which would lead to the alter-The intermediate is then saponified and nate diene. alcohol at C-17 oxidized (48). Elimination of the angular methyl group at C-19 with consequent aromatization is achieved by treatment of the diene with lithium in the presence of diphenyl;¹⁵ there is thus obtained 7α -methyl estrone (49).¹⁶ Methylation of the phenolic hydroxyl group followed by reduction of the 17-ketone gives 50. Birch reduction affords the corresponding 2,5(10)-diene (51). The hydroxyl at 17 is then oxidized by means of cyclohexanone and aluminum isopropoxide (Oppenauer oxidation) to give back the 17-ketone (52). Addition of lithium acetylide proceeds to give the 17α -ethynyl derivative (53). Hydrolysis of the enol ether under mild conditions leads to the unconjugated ketone. There is thus obtained the anabolic agent tibolone (54).¹⁷

















(<u>53</u>)



(<u>54</u>)

Inclusion of a methyl group at the difficultly accessible ll-position also proves compatible with oral progestational activity in the 19-nor series. Preparation of an agent incorporating this feature starts with the 1,4-diene (55), corresponding to adrenosterone.¹⁸ Due to the sterically hindered nature of the carbonyl at C-ll and the low reactivity of that at C-3, ketalization proceeds selectively at C-17 (56); reduction of the ll-keto group by means of lithium tri-t-butoxyaluminum hydride gives intermediate Aromatization by means of the lithium radical 57. anion from diphenyl gives intermediate 58.19 Methylation of the phenol (59) followed by oxidation of the alcoholic hydroxyl at C-ll affords 60. Addition of methyl Grignard reagent to that carbonyl group serves to introduce the ll-methyl group (61). It is of note that the corresponding reaction in the 19methylated (androstrane) series proceeds with extreme reluctance. Deketalization gives the corresponding 17-ketone and acid catalyzed dehydration, followed by catalytic reduction of the olefin (62), gives the intermediate containing the 11β -methyl group (63). That molecule is then subjected to the standard carbonyl reduction, Birch reaction, oxidation, ethynylation and, finally, hydrolysis sequence (see Hydrolysis of the enol ether under more 50 to 53). strenuous conditions than was employed with 53 gives the conjugated ketone 65. The carbonyl group is then reduced to afford the corresponding 3β -alcohol (66). Exhaustive acetylation affords the potent oral progestin methynodiol diacetate (67).























Elaboration of a commercially viable route for total synthesis of 19-nor steroids led to the introduction of the totally synthetic product norgestrel (71) as the progestational component of an oral contraceptive. As was observed in the "natural" 19nor-compounds, reduction of the 17-ethynyl group to 17ethyl affords compounds with androgenic/anabolic activity. Oppenauer oxidation of the total synthesis intermediate 68^{22} leads to the corresponding ketone. Reaction with ethylmagnesium bromide gives the expected condensation product. It is of note that reaction is much slower than in the 13-methyl series. Hydrolysis with strong acid affords norbolethone (70).²¹ The same compound can be obtained by selective reduction of the ethynyl moiety of norgestrel (71).













(<u>71</u>)

In much the same vein, acetylation of optically active *d*-norgestrel by means of acetic anhydride and tosic acid gives the 17-acetate (72). Reaction with hydroxylamine hydrochloride in pyridine affords the orally active progestin *dexnorgestrel acetime* (73).²³

The prevalence of 17-ethynyl carbinols among the orally active 19-nor progestins can lead to the impression that this is a necessary group for activity. The good potency shown by a compound that possesses the 17-hydroxy 17-acetyl moiety more characteristic of the 19-methyl progestins indicates that the structureactivity relationship is not quite that narrow. One such compound, gestonorone caproate (85) is prepared by oxidation of 16-hydropregnenolone $(74)^{24}$ to afford the conjugated ketone 75. This is then converted to the aromatic A-ring phenol 77 by the standard dehydrogenation-aromatization scheme (see 47 to 49). Epoxidation of the double bond at C-16 by alkaline peroxide gives the 16α , 17α -oxide 78. Methylation of the phenol affords the corresponding ether (79). Trans-diaxial opening of the oxide by means of hydrogen bromide gives the bromohydrin 80; halogen is then removed reductively by means of zinc in acetic acid The carbonyl group at C-20 is next protected (81).against the reductive conditions of the subsequent step by conversion to its ethylene ketal (82). Birch reduction leads in the usual way to the enol ether (83). Treatment with strong acid serves to remove both the 20-ketal and the enol ether at C-3, leading to conjugated ketone 84. Treatment of this last intermediate with caproic anhydride and tosic acid affords

gestonorone caproate (85).²⁵ The caproate function not only contributes lipophilicity but, presumably, Newman-type hinderence to saponification.



2. ANDROSTANES

Additional unsaturation at C-1,2 is well known to potentiate the action of both androgens and corticoids. The former tend, however, to show poor oral activity in the absence of an alkyl group at the 17-position. Thus, they tend to be used mainly as injectable agents. As mentioned above, esterification with a fatty chain leads to agents with long duration of action. Thus, esterification of 86^{26} with the acid chloride from undec-10-enoic acid gives the injectable anabolic agent *boldenone 10-undecylenate* (87).²⁷ An

enol ether, interestingly, can serve a similar pharmacological purpose. Thus, acetal interchange of 86 with the diethyl acetal from cyclopentanone gives 88; pyrolysis leads to elimination of ethanol and formation of *quinbolone* (89).²⁸



Neoplasms involving gonadal tissues are often dependent on sex hormones for growth. Depriving the cancerous growth of hormonal stimulation frequently slows its development. The past few years have seen considerable application of hormone antagonists as antineoplastic agents for treatment of such hormonedependent cancers. Bolasterone (91) is known to be a potent anabolic/androgenic agent; its 7 β -isomer, calusterone, has found some use in the treatment of cancer. As originally prepared, conjugate addition of methylmagnesium bromide to diene 90 affords a mixture of 91 and 92 with the former predominating. Calusterone (92) was separated by chromatography and fractional crystallization.²⁹



Formal isomerization of the double bond of testosterone to the 1-position and methylation at the 2-position provides yet another anabolic/androgenic Mannich condensation of the fully saturated agent. androstane derivative 93 with formaldehyde and dimethylamine gives aminoketone 94. A/B-trans steroids normally enolize preferentially toward the 2-position, explaining the regiospecificity of this reaction. Catalytic reduction at elevated temperature affords the 2α -methyl isomer 95. It is not at all unlikely that the reaction proceeds via the 2-methylene intermediate. The observed stereochemistry is no doubt attributable to the fact that the product represents the more stable equatorial isomer. The initial product would be expected to be the β -isomer but this would experience a severe 1,3-diaxial non-bonded interaction and epimerize via the enol. Bromination of the ketone procéeds largely at the tertiary carbon adjacent to the carbonyl (96). Dehydrohalogenation by means of lithium carbonate in DMF affords stenbolone acetate (97).³⁰ This product is readily separable from a number of by-products by the fact that it forms a water-soluble bisulfite adduct.



Contraction of the B-ring of the orally active androgen 17-methyltestosterone, interestingly, leads to a compound with antiandrogenic activity. The general method for preparation of such ring contracted analogues was first developed using cholesterol acetate (98) as a model. Oxidation by means of chromium trioxide affords keto acid 99 as the principal product; this is then converted to the enol lactone 100 by means of acetic anhydride. Pyrolysis of that enol lactone at 200°C gives the ring contracted condensation product 101.³¹ The analogous 17-ketone 102 is used as starting material for the antiandrogen. Reaction with an excess of methylmagnesium bromide affords the 17-methylcarbinol 103; Oppenauer oxidation affords benorterone (104).³²



Fusion of a heterocyclic ring onto the A-ring of ethynyltestosterone leads to a compound with hormone antagonistic activity. Such agents find some use in those cases where either the given hormone is present in excessive amounts by malfunction of the particular endocrine gland or where it is desirable to suppress hormonal stimulation of some end organ. Condensation of 17-ethynyl testosterone (105) with ethyl formate in the presence of sodium methoxide gives the corresponding 2-hydroxymethylene derivative (106). Reaction of that intermediate with hydroxylamine leads to the pituitary suppressant agent danazol (107).³³



A somewhat related sequence leads to *trilostane* (*111*), a compound that inhibits the adrenal gland; more specifically the agent blocks some of the metabolic responses elicited by the adrenal hormone ACTH in experimental animals. Reaction of the hydroxymethylene derivative *108*, obtained from testosterone, with hydroxylamine gives the corresponding isoxazole (*109*). Oxidation of the C-4,5 double bond by means



of mCPBA proceeds from the less hindered side to give the α -epoxide. Treatment of the intermediate 110 with sodium methoxide leads to scission of the heterocycle and formation of the corresponding cyanoketone 111. It is of interest that the epoxide is apparently inert to these conditions; the nitrile is of course readily epimerized, and thus assumes the more stable α (equatorial) conformation. There is thus obtained trilostane.³⁴ The ring opening can be rationalized by assuming first formation of the anion 112; electrocyclic rearrangement as shown gives the enolate anion of 111.

Fusion of a heterocyclic ring onto the A-ring of a molecule which shows mainly progestational activity leads to an antiinflammatory agent; this finding does not seem to have been followed up to any extent. Condensation of 17-ethynyl testosterone (113) with ethyl formate in the presence of base gives the corresponding 2-hydroxymethyl derivative (114). Reaction of that with p-fluorophenylhydrazine affords the antiinflammatory pyrazolone *nivazol* (115).



159

The antineoplastic agent testolactone (121) appears to be obtained commercially by microbiological transformation of either testosterone or progesterone. The compound can be obtained synthetically, albeit in low yield, starting from dehydroepiandrosterone (116a). Addition of bromine serves to protect the double bond as the dibromide (117). Oxidation with peracetic acid gives the Baeyer-Villiger product 118. The unsaturation at 5,6 is then restored by treatment of the dibromide with sodium iodide (119). This is oxidized to the conjugated ketone 120 under Oppenauer conditions. (A real source of confusion exists in the fact that 120 bears the trivial chemical name testolactone while the same generic name is used to denote 121.) Previous work, particularly on cortical steroids, had shown that inclusion of additional unsaturation in the A ring at 1,2 leads to a significant increase in potency. Selenium dioxide is a fairly specific reagent for achieving this transformation, and such treatment of 120 affords testolactone (121). 36



160

It has been known for many years that elevated levels of serum cholesterol are associated with atherosclerosis, although the cause-effect relationship remains unproven. A rather straightforward therapeutic regimen intended for prevention or arrest of the progress of this disease involves lowering levels of serum cholesterol in the high-risk population. Since a good part of the physiological cholesterol load is provided by endogenous synthesis, agents that inhibit this process should lower cholesterol levels in the serum as an adjunct to dietary precautions, although a compensatory increase in endogenous synthesis can combat this artifice. One approach to this therapeutic goal consists in providing false substrates for enzyme systems involved in cholesterol biosynthesis. Substitution of heteroatoms for carbon has served to provide such enzyme antagonists in other fields. The strategy in the case at hand calls for a cholesterol analogue containing nitrogen in the side chain. Shiff base formation between dehydroepiandrosterone acetate (116b) and 3-dimethylaminopropylamine affords imine 122. Reduction (lithium aluminum hydride) proceeds to give predominantly the β -amine (123). Further methylation by means of formic acid and formaldehyde (Eschweiler-Clark reaction) leads to azacosterol (124).³⁷ Though the compound does lower serum cholesterol in experimental animals it is not used clinically in man. The drug, not unexpectedly, severely limits cholesterol availability in avian species. Since egg formation in birds is dependent on an abundant supply of cholesterol, azacosterol is, in

fact, an effective avian chemosterilant. A glance at the formula of cholesterol (124a) clearly shows the bioisosterism used in the design of 124.



The crude toxin *curare*, used by South American Indians to lend authority to their blow gun darts, proved, because of its neuromuscular blocking activity, to be of interest to surgeons. Structural analysis of the mixture led to the erroneous conclusion that the active agents possessed a pair of quaternary nitrogen atoms with definite spacing because of the rigid molecular framework. Following the rationale based on this belief led to a number of curarelike synthetic agents in which the spacing is provided by aliphatic chains; it is readily apparent that the rigid network provided by a steroid would provide more accurate location of the charged centers. The synthesis of one of these starts with conversion of *125* (probably obtained by dehydration of the corresponding 3hydroxy compound) to the enol acetate (126). Epoxidation proceeds as expected from the α side to give the bis epoxide (127). Both regio- and stereochemistry of the subsequent reaction with piperidine are dictated by the diaxial opening propensity of oxiranes; the hemiacetal-like function left at C-17 spontaneously reverts to the ketone to give 128. Reduction of that ketone proceeds in the usual manner to afford 129. Acetylation of the hydroxyl groups (130), followed by quaterization with methyl bromide gives pancuronium bromide (131).³⁸



3. PREGNANES

a. 11-Desoxy Derivatives

Progesterone, 132, is, of course, the prototype pregnane. This natural steroid plays an important role in females in the intricate endocrine chain of events involved in reproduction. In essence, progesterone is one of the steroid hormones directly involved in the timing of ovulation. Very high levels of progesterone are present in early pregnancy, elaborated biosynthetically by a structure on the ovary (the corpus luteum), and this inhibits ovulation in the gravid female to prevent a superimposed pregnancy. It is this observation that gave initial direction to the development of the oral contraceptives. As with the estrogens, much of the work described below was carried out before a shadow fell on this class of drugs. In addition, there was some evidence from human trials that a potent progestin could provide contraceptive activity in the absence of added estrogen. Although the efficacy was somewhat lower than for the combination Pill, the treatment avoided the use of the suspect estrogenic component. The finding that many potent progestins cause tumerous lesions in the beagle on long-term administration effectively laid this class of drugs to rest as far as large-scale usage is concerned. It can be argued quite reasonably that this effect is restricted to the beagle, but expert opinion is divided and use has subsided.

As described earlier, oral activity can be achieved in the progestins by either removing the 19-
methyl group or inclusion of an acyloxy group at the 17-position. It is of interest that removal of the oxygen function at C-3 is compatible with biological activity in both series (see 37, 39, this Chapter). Thus, the 3-desoxy analogue of medroxyprogesterone acetate shows very similar activity to the parent substance. Reaction of medroxyprogesterone $(133)^{39}$ with ethanedithiol gives the corresponding thicketal (134). Desulfurization by means of Raney nickel leads to the 3-desoxy steroid (135). Treatment with acetic acid in the presence of trifluoroacetic anhydride completes the synthesis of angesterone acetate (136).



Chlormadinone acetate (137), ⁴¹ is an extremely potent orally active progestin. Treatment of this compound with basic sodium borohydride serves to reduce the ketone at C-3 to the corresponding 3carbinol (138; the regioselectivity is presumably due

to the more hindered environment about the 20-ketone). Acetylation affords *clogestone* (139). ⁴² Further dehydrogenation of the A ring of *chlormadinone* by means of selenium dioxide affords *delmadinone acetate* (140). ⁴³



Fusion of a cyclopropyl ring onto the 1,2position of chlormadinone gives a compound which, interestingly, shows mainly antiandrogenic activity. Preparation of cyproterone acetate (146) starts by reaction of triene 141 (obtainable from 17-acetoxyprogesterone⁴⁴ by sequential dehydrogenations at C-5,6 and C-1,2) with diazomethane affords the pyrazoline (142). Pyrolysis leads to the cyclopropyl derivative (143) by loss of nitrogen.⁴⁵ Oxidation by means of perbenzoic acid gives the C-6,7 epoxide (144). Regioselectivity in this reaction is probably due to conjugate addition of peracid from the α side followed by electron backflow and ejection of benzoate as shown in 143a. Reaction of that intermediate with hydrogen chloride serves to open both the oxirane and cyclopropyl rings. The intermediate chlorohydrin is not observed as it undergoes spontaneous dehydration

to 145. Treatment of the chloromethyl derivative with collidine serves to reform the cyclopropyl ring; the reaction very probably goes by internal alkylation of the anion generated by the base at the 2-position. There is thus obtained cyproterone acetate (146). 46



Inclusion of an additional fused cyclopropane ring at C-16,17 gives a compound in which progestational activity is said to predominate. Saponification of the acetate in 143 gives the corresponding 17-alcohol (147). Heating in refluxing quinoline results in dehydration with formation of the 16,17-olefin (148). Reaction with diazomethane gives the pyrazoline (149), which on heating in acid affords the biscyclopropyl derivative (150). This compound is then taken on to the 6-chloro analogue by a sequence identical to that used to prepare 146. There is thus obtained the progestin gestaclone (151). 47,48



Substitution by a methyl group at the 16-position is known to have a marked potentiating effect in the corticosteroid series. Combination of such a group with the unsaturated 6-chloro group in the progesterone series affords an extremely potent progestin. One route for preparation of the starting material for this drug consists in first introducing the 17hvdroxvl. Thus, the ketone at C-17 in the progesterone derivative 152 (obtainable from the corresponding pregnenolone 165) is converted to the enol acetate (153). The next step in this so-called Gallagher chemistry consists in conversion of the enol double bond to the epoxide to give 154. Hydrolytic ring opening gives initially the hydroxy hemiacetal acetate; this quickly goes on to the hydroxy ketone (155).



After protection of the C-20 keto group as the dioxolane (156), the 3-acetyl group is saponified and the resulting alcohol (157) is oxidized to the ketone (158). Bromination (159) followed by dehydrobromination introduces the required 4-ene-3-one functionality (160); removal of the ketal would then afford the required starting material (161). Heating of 161 in the presence of chloranil then introduces the desired unsaturation at C-6,7. A sequence identical to that used to prepare 146 (epoxidation; hydrogen chloride) is then used to introduce the 6chlorine atom⁵⁰ and the progestin *clomegestone acetate* (164) results.

The analogue of 164 lacking unsaturation at C-6 and oxygen at C-17 unexpectedly shows antiestrogenic rather than progestational activity. Pregnenolone analogue 165^{49} is starting material for this analogue as well. Chlorination of the double bond by means of chlorine in pyridine affords the dihalo derivative The stereochemistry is best rationalized by 166. assuming chloronium ion formation on the less-hindered α -side followed by diaxial opening of that ring by chloride ion. Oxidation of the alcohol (167) affords the 3-keto derivative (168), and reaction of that with sodium acetate leads to dehydrochlorination, yielding the enone (169). Exposure of that intermediate to mild acid isomerizes the halogen substituent to the more stable equatorial 6*α*-position and produces clometherone (170).⁵¹



Yet another observation that carries over from the corticoids to progestins is the potentiation observed by formation of acetonides from the 16,17glycols. It is of note in this case that the parent glycol itself fails to show activity in the standard progestational assay. Treatment of the progesterone derivative 172 (available by oxidation of 16-dehydropregnenolone (171) with potassium permanganate) with acetone affords the 16,17-cyclic acetal algestone acetonide (173); ⁵² in the same vein, reaction with acetophenone yields algestone acetophenide (174). 53 Although formation of the latter involves the creation of a new chiral center, only one isomer is in fact isolated from the reaction. Since acetal formation is accomplished under thermodynamic conditions, the more stable isomer involving the least steric crowding

should prevail. It has been proposed that the configuration of 174 is that which carries the aromatic ring oriented away from the steroid molecule (174a). Earlier work had shown that the presence of the 17hydroxyl substituent is crucial for oral activity in the 21-carbon progestin series; progesterone itself



shows poor activity on oral administration. This key group can be replaced by halogen with retention of oral activity. Bromination of pregnenolone acetate (175a) in acetic acid gives the tetrabromide 175b. Treatment with sodium iodide leads to both elimination of the 5,6-dibromide grouping and displacement of the α -keto halide at C-21 by iodine; there is obtained dihalide 176. Reduction of the haloketone with bisulfite gives the methylketone 177;⁵⁴ the selectivity is probably due to both the greater reactivity of iodine and the greater steric accessibility of

that group. Saponification to 178 followed by treatment with peracid gives the 5,6-oxide 179. Diaxial ring opening of the oxirane with HF leads to the *trans*fluorohydrin 180. Oxidation of the hydroxyl at C-3 by means of Jones reagent then affords hydroxyketone 181. Treatment of this last with acid serves both to generate the enone, by dehydration of the tertiary carbinol, and to invert the fluoro group at C-6 to the more stable equatorial, 6α -configuration. There is thus obtained haloprogesterone (182).⁵⁵



Aldosterone (183) is one of the key steroid hormones involved in regulation of the body's mineral and fluid balance. Excess levels of this steroid quickly lead to marked retention of sodium chloride, water and, often as a consequence, hypertension. The aldosterone antagonist *spironolactone* (184)⁵⁶ has proven of great clinical value in blocking the effects

of hyperaldosteronism. In addition, the drug has proven an effective diuretic and antihypertensive agent even in those cases where no gross excesses of aldosterone can be demonstrated. It is of note that the immediate chemical precursor of *spironolactone* (184), diene 185 was in fact found to be one of the active metabolites of that drug in the body. The diene, *canrenone* (185) now constitutes a drug in its own right. Both this and the following aldosterone antagonists are also available in the form of the potassium salt of the ring-opened hydroxy acid; in this case, *potassium canrenoate* (186).



Cyclopropanation of the 4,6-diene function proceeds selectively at the 5,6-double bond. Thus, reaction of 185 with the ylide from trimethyl sulfonium iodide and sodium hydride, in DMSO, affords predominantly the α -cyclopropyl compound (187) accompanied by traces of the β -isomer. The lactone constitutes the diuretic-antihypertensive prorenone;⁵⁷ the ringopened salt is known as potassium prorenoate.

Introduction of a carbomethoxy moiety at C-7 should afford a nonreversible counterpart of 184. To effect this, addition of cyanide to the extended conjugated system in 185 leads to addition of two moles of the nucleophile; there is obtained the unusual bicyclic intermediate 190. The reaction may be rationalized by assuming that addition occurs initially at the terminus of the system to give 188 This, however, under the reaction as expected. conditions chosen, undergoes addition of the second mole of cyanide which, of necessity, goes through anion 189; reaction of the negative charge at C-4 with the nitrile at C-7 would lead to the observed product (190). This can only happen following β addition of cyanide. Hydrolysis of the imine function proceeds to give diketone 191. A conformational drawing (191a) shows that the molecule is by no means as strained as the planar projection would suggest. Reaction of 191 with methoxide reverses the formation of the additional ring. The reaction sequence probably starts by addition of methoxide to the carbonyl group (192); collapse of the alkoxide anion gives the intermediate anion 193, which neutralizes itself by facile elimination of the excellent leaving group, cyanide. There is thus finally obtained mexrenone (194);⁵⁸ the salt is known as potassium mexrenoate.



b. 11-Oxygenated Pregnanes

The story of the discovery of the utility of cortisone as an antiinflammatory agent has been told often enough not to need full repetition here.⁵⁹ In brief, cortisone is one of the more important hormonal steroids elaborated by the adrenal cortex; this steroid is intimately involved in the regulation of a host of biological processes such as, for example, regulation of glucose utilization and mineral balance. Administration of doses far in excess of those required for hormonal

action were found to alleviate the symptoms of a multitude of conditions marked by inflammation. When used for this purpose, the normal hormonal effects are undesirable. These side effects are, however, seen to be natural extensions of the hormonal action. Immediately following this discovery, an enormous effort was mounted in the laboratories of the pharmaceutical industry aimed at separation of the antiinflammatory activity of these molecules from their hormonal activities. The most visible outcome of this work was a tremendous increase in the milligram potency achieved by various structural modifications. Drugs were produced that, in addition, had changed hormonal spectra; some such steroids had more pronounced effects on glucose metabolism ("glucocorticoids"), whereas others were more effective in changing mineral balance ("mineralocorticoids"). Despite this, no steroid truly devoid of hormonal activity rewarded these efforts. The full realization of the clinical deficiencies of the corticoids, coupled with the increasing availability of nonsteroidal antiinflammatory agents, has led to a great decrease in routine use of these drugs in medical practice. It is for that primary reason that the compounds discussed next failed to have greater medical and economic impact. It is of note that this work represented an unparalleled effort on the part of medicinal chemists, both as to the complexity of the molecules involved and the length of the synthetic schemes utilized. In some ways this foreshadowed the current prostaglandin programs, both in the goal

(splitting of activities) and in chemical sophistication (in fact, the same names often appear as authors in the late steroid papers and early prostaglandin publications).

As has been mentioned, preparation of esters of the C-17 hydroxyl group of selected progestins affords compounds with prolonged action. Similar chemical treatment of a corticoid would almost certainly lead to an ester of the sterically more accessible primary alcohol at C-21. In an interesting method for achieving esterification of the more hindered and less reactive tertiary 17-hydroxyl, *prednisolone* $(195)^{59}$ is converted to a mixture of the diasteromeric cyclic ortho esters (196) by ester interchange with trimethyl ortho-pentanoate. Acid-catalyzed dioxolane ring opening proceeds by protonation of the more





(196)

(<u>195</u>)



(<u>197</u>)

sterically accessible oxygen attached to the 21position. There is thus obtained *prednival* (197).⁶⁰ It is of interest that 197 rearranges to the 21-ester on heating, representing an 0-to-0 acyl migration.

It was found quite early in the steroid effort that inclusion of several groups, which singly potentiated activity had an additive effect; for example, a cortisone derivative that included both the unsaturation at C-1,2 and a methyl group at C-6 would be more potent than the derivative that possessed either group alone. Much of the chemical strategy thus devolved on designing routes which would permit the inclusion of combinations of potentiating groups.

Dehydration of cortisone (198) affords the diene 199. This is then converted to ketal 200. The selectivity is due to hindrance about both the 11- and The shift of the double bond to 20-carbonyl groups. the 5.6-position is characteristic of that particular Treatment of protected diene 200 with osmium enone. tetroxide results in selective oxidation of the conjugated double bond at C-16,17 to afford the cisdiol (201). Reduction of the ketone at C-11 (202) followed by hydrolysis of the ketal function gives the intermediate 203.61a Selenium dioxide has been found empirically to dehydrogenate such 3-keto-4-ene steroids to the corresponding 1,4-dienes. (See, for example, 120-121 and 137-140.) Thus in the case at hand, reaction of 203 with selenium dioxide gives the diene 204.^{61b} Reaction of the *cis*-diol function with acetone forms the cyclic acetal and, thus, the corticoid desonide (205).62



An analogous sequence starting with 6β -fluorocortisone (206),⁶³ but omitting the selenium dioxide dehydrogenation, affords *flurandrenolide* (207).⁶⁴

Microbiological oxidation has proven of enormous value in steroid chemistry, often affording selective means of functionalizing remote and chemically inactivated positions. It will bear mentioning that the ll-oxygen for all commercially available corticoids is in fact introduced by such a reaction carried out on plant scale. Preparation of the l-dehydro analogue of 207 involves biooxidation to introduce the l6-hydroxyl. Incubation of 6α -fluoroprednisolone

 $(208)^{63}$ with Streptomyces roseochromogenes effects α -hydroxylation at the 16-position (209). Reaction with acetone affords the corticoid flunisolide (210).⁶⁵



The 6-chloro-6-dehydro moiety apparently has a similar potentiating effect on corticoids as it does on progestins. One scheme for preparing the requisite starting 6-chloro compound begins with the opening of oxide 211 with hydrogen chloride to give halohydrin 212. Reduction of the 21-ester function by means of lithium aluminum hydride, followed by acetylation, gives 213. Transformation of the 17,20-olefin to the requisite hydroxyketone grouping is achieved by a combination of osmium tetroxide and N-morpholine oxideperoxide (NMOP) treatments. The reaction sequence presumably starts by hydroxylation of the olefin via the osmate ester; the secondary alcohol at C-20 is then further oxidized to the ketone by the NMOP. The latter also served to reoxidize the osmium reagent from the dioxide to the tetroxide, allowing that expensive and toxic reagent to be used in catalytic quantities. Deketalization (215) followed by acid



catalyzed dehydration affords the conjugated ketone (216).⁶³ The remaining unsaturation at C-1 and C-6 is then introduced either by sequential treatment with selenium dioxide and chloranil or under special conditions with chloranil alone. Saponification of the acetate affords the corticoid *cloprednol* (218).⁶⁶

Although oxygenation at C-ll seems to be required for activity in the corticoid series, the presence of that function is not incompatible with progestational activity.⁶⁷ Thus, perhaps surprisingly in view of some corticoids discussed below, mere lack of the hydroxyl group at C-21 seems, in at least one case, to give a compound which exhibits progestational activity. Microbiological oxidation of diketone epoxide 219 by means of Rhizopus nigricans affords the corresponding $ll\alpha$ -hydroxy derivative (220). Dehydration of this via the mesylate (221) gives the 9,11-olefin (222). Ring opening of the oxirane moiety by means of hydrogen iodide gives the halohydrin 223. Treatment with zinc in acid serves to remove the halogen reductively (224); the 17-hydroxy group is then acetylated by means of acetic anhydride in the presence of tosic acid to give 225. The 11β -hydroxy-9a-halo function is associated with most potent corticoids; the manner of introduction used in this case well illustrates the relatively standard sequence used to incorporate this function. Addition of the elements of HOBr to the double bond is usually accomplished by N-bromosuccinimide in aqueous base. Both regio- and stereospecificity are no doubt guided by the initial formation of the 9α , 11α -bromonium ion, followed by nucleophilic diaxial opening to give 226. Treatment of the bromohydrin with base leads to the formation of the β -oxide (227) by intramolecular displacement of halogen by the neighboring alkoxide ion. Addition of hydrogen fluoride to the oxide proceeds with diaxial opening to afford the 9a-fluoro- 11β -hydroxy functional array. In the case at hand there is formed the progestin *flurogestone* acetate (228).⁶⁹ This drug has been in use for controlling the estrus cycle in domestic animals under the name Equamate®.



The presence of an additional carbon atom on the dihydroxyacetone side chain is quite compatible with. antiinflammatory activity. Oxidation of 9α -fluoprednisolone $(229)^{70}$ by means of cupric acetate affords the corresponding 21-aldehyde (230). Addition of diazomethane to the aldehyde serves to lengthen the side chain as the epoxide 231. Opening of the oxirane ring with hydrogen bromide occurs regioselectively to give the 22-bromo derivative (232). Heating of the bromohydrin leads to loss of hydrogen bromide with formation of the alpha diketone (233) (this reaction can be rationalized as loss of HBr to give the enol followed by ketonization). Reduction of the side chain diketo alcohol by means of yeast proceeds both regio and stereospecifically to give the derivative containing the 21 α -hydroxyl group (234). Acetylation under mild conditions then affords the antiinflammatory steroid fluperolone acetate (235).⁷¹



The potentiating effect of the 16-hydroxyl group in the corticoid series has been mentioned previously. The acetonide of such a steroid, *triamcinolone* (237), is in fact one of the more widely used corticosteroids. The nature of the group used to form a ketal apparently has only relatively minor influence on biological activity. Reaction of the 16,17-glycol 236^{72} with 3-butanone yields *amcinafal* (238);⁷³ in the same vein condensation with acetophenone leads to *amcinafide*

(239).⁷³ The ketal stereochemistry is not specified. Unsaturation in the A ring has been usually assumed to be necessary for biological activity; the reader will have noted the high prevalence of 1,4-dienes. It is interesting therefore to note that the analogue possessing a fully saturated A ring is apparently quite active in its own right. Thus, catalytic reduction of 237 affords the corticoid drocinonide (240).⁷⁴





It is of interest that there exists a considerable amount of flexibility as to the substituent at C-21 in the acetonide series. For example, formation of the acetonide from 241^{72} affords intermediate 242. Reaction with methanesulfonyl chloride gives the corresponding mesylate (243). Displacement

of the ester with lithium chloride in DMF gives the corticoid halcinonide (244).⁷⁵



The C-21 substituent can in fact be dispensed with entirely. Perhaps because descinolone acetonide (254) predates 244 by better than a decade, the synthetic sequence reported for its preparation is quite complex. Although descinolone (253) could in principle be prepared in a few steps from some currently available starting materials, such as 241, the original synthesis is presented for its heuristic value.

Epoxyketone 245 is readily available from 16dehydropregnenolone via several steps, including a crucial microbiological ll α -hydroxylation. Dehydration of 245 gives the 9,ll-olefin 246. The alcohol at C-21 is then converted to the mesylate (247), and this is reduced to give the methyl ketone (248). The olefin is then converted to the 9 α -fluoro-ll β -hydroxy array (250) by the standard sequence [addition of HOBr, closure to the oxirane (249), opening with HF]. Note that the reactivity of the epoxides in 249 is













(254)





sufficiently different so that reaction occurs regioselectively at C-9,11. The remaining major transformation is the establishment of the 16α , 17α -glycol function; this cannot be readily achieved from 250 since this would demand the *cis*-opening of an oxirane. Deoxygenation of the epoxide with chromous chloride gives back the 16,17-olefin (251). In effect the epoxide has been used in this sequence as a protecting group for an olefin. Hydroxylation with osmium tetroxide gives the desired glycol (252); microbiological dehydrogenation (using Nocardia corallina) serves to introduce the double bond at C-1 (253). Reaction with acetone finally affords descinolone acetonide (254), 76 an antiinflammatory agent.

Although the Vilsmeier reaction is known best in aromatic systems, aliphatic olefins also undergo formylation. Synthesis of formocortal (257) involves such a step. Formation of the monoketal of 255 involves the 3-ketone function with the familiar concomitant shift of the double bond to C-5,6. Reaction of 256 with phosphorous oxychloride and DMF involves first formylation at the 6-position; opening of the ketal to the enol ether by the HCl produced in the Vilsmeier reaction would afford a hydroxyethyl side chain at C-3. This is no doubt converted to a chloroethyl group by excess oxychloride. There is thus obtained the antiinflammatory agent formocortal (257).⁷⁷

As is the case with other classes of steroids, inclusion of nitrogen atoms into corticoids has met with only limited pharmacological success. Compounds containing a pyrazole ring fused onto the A ring have, however, shown sufficient activity to merit generic names. Synthesis of the requisite intermediate for its incorporation starts with the protection of the dihydroxyacetone side chain. Reaction of 258 with formaldehyde gives the internal double acetal 259. (This bismethylenedioxyether-protected (259a) function is known as BMD for short.) Dehydrogenation by means of chloroanil proceeds in the usual way to give the 4,6-diene (260). Formylation with ethyl formate and sodium hydride leads to 261.



Condensation with phenylhydrazine results in phenylpyrazole 262. The regiospecificity results from intermediate phenylhydrazone formation of the more

reactive aldehyde function. The sequence is completed by deprotection of the cortical side chain by acid hydrolysis (263), followed by acetylation of the 21-hydroxy group. There is thus obtained the corticoid cortivazo1 (264).⁷⁸

Inclusion of halogen, particularly fluorine, at either the C-6 or C-9 positions in the cortisone molecule is well known to increase potency. Combination of these potentiating groups in the same molecule in general leads to an additive influence on potency. The synthesis of one such compound, difluprednate (271), starts with a scheme analogous to that used to The C-17,21 diol 265 is first converted prepare 197. to the cyclic ortho-ester (266) by means of methyl ortho-butyrate. Cautious hydrolysis affords the 17-butyrate ester (267). Exhaustive acetylation leads to reaction not only at C-21, but formation of the enol acetate at C-3 as well (268). Reaction of that intermediate with perchloryl fluoride (FClo₂) leads to halogenation at the terminus of the electronrich diene system. Work-up gives a mixture of the epimeric 6-fluoro compounds; equilibration in acid provides the more stable equatorial 6α -isomer (269). The 9,11-diene is then taken on to the 9α -fluoro-ll β hydroxy function by the standard reaction sequence (270). Dehydrogenation by means of DDQ completes the synthesis of difluprednate (271). 79

Omission of the 17-hydroxyl group in the 6,9dihalo compounds apparently does not lead to loss of biological activity. Dehydration of the 6α -fluoro-17desoxy intermediate 272^{80} by means of NBS in pyridine







leads to the 9,11-olefin (273). This is then converted to the halohydrin by the standard sequence. Microbiological dehydrogenation of the A ring leads to the 1,4-diene. There is thus obtained the antiinflammatory steroid diflucortolone (275).⁸¹

Although the most common substituent found at the C-9 position in the commercially available corticoids is fluorine, the initial observation of the



potentiating effect of halogen was in fact made with chlorine at that spot. It is thus of interest to note that one of the more recent 17-desoxy-6,9-dihalo cortocoids contains chlorine at C-9. Starting material for that compound is 16-methyl steroid 276.82 Τn distinct contrast to previous work, the desired halohydrin is introduced in a convenient single step rather than by the usual three-step sequence. Thus, reaction of the olefin with tertiary butyl hypochlorite in the presence of perchloric acid affords directly the 9α -chloro-ll β -hydroxy function and, thus, clocortolone (277), an antiinflammatory agent. It is not unlikely that the actual reagent is HOCl; attack on the 9,11-olefin by Cl⁺ would occur from the less hindered side to give the 9α , 11α -chloronium intermediate. Attack of OH to give diaxial ring opening would lead to the observed halohydrin.





The scheme required to prepare the potent trifluoro corticoid cormethasone acetate (292) illustrates the synthetic complexities involved in some of this work. Sequential acetylation of the pregnenolone derivative 278 with first acetic anhydride in pyridine and then acetic anhydride in the presence of tosic acid affords diacetate 279. Reaction of that intermediate with nitrosyl fluoride results initially in addition of the reagent to the 5,6-olefin moiety to afford the fluoro oxime; reaction with a second mole of reagent at nitrogen gives the nitroimine derivative 280; passage over alumina serves to hydrolyze the imine function to the corresponding 6-ketone (281).









 $(\frac{286}{282})$ R = COCH₃ $(\frac{282}{282})$ R = H









Sulfur tetrafluoride in hydrogen fluoride has been developed as a selective and general reagent for converting ketones to the corresponding difluoromethylene groups. Application of that reaction to 281 gives the desired 6,6-difluoro derivative 282. The less-hindered acetate at C-3 is then hydrolyzed selectively (to 283); bromination in dioxane leads to the 21-bromo derivative 284. Jones oxidation gives the 3-ketone (285). Reaction of that compound with silver acetate serves to displace the bromine by acetate, to introduce the enone function by elimination of hydrogen fluoride, and to hydrolyze the 17-acetate. There is thus obtained 286. Saponification of the remaining 21-acetate gives the desired intermediate 287. Successive microbiological oxidation with Curvularia lunata and Arthrobacter simplex serves to introduce respectively the 11β hydroxyl (288) and 1-olefin functions (289). Reacetylation (290) followed by dehydration gives the required 9,11-olefin (291). This is converted to the 9,11-fluorohydrin by the standard sequence to afford finally cormethasone acetate (292).⁸³

The recurring theme in work on corticoids discussed thus far with the exception of the 17-desoxy compounds consisted in the introduction of additional functions to the basic cortisone molecule. Some further success in producing biologically active molecules has been achieved by substituting unnatural functions for those present in the protoype molecule. Thus the hydroxyl groups at both C-11 and C-21 can be replaced by halogen with retention of activity.



Reaction of the olefin (294), corresponding to fludrocortide (293),⁸⁴ with chlorine affords directly flucloronide (295).⁸⁵ The stereochemistry can, as in the case of 277, be rationalized by invoking the intermediacy of the 9α ,ll α -chloronium ion. Reaction of 294 with methanesulfonyl chloride affords the corresponding mesylate (296); displacement of the ester by means of lithium chloride affords the 21-chloro intermediate (297). Addition of chlorine to the 9,11-double bond gives triclonide (298).⁸⁶ A similar sequence on the tosylate (299), leading through the intermediate fluoride (300), gives the antiinflammatory agent tralonide (301).⁸⁷

Antiinflammatory activity also persists in the absence of oxygen at either C-17 or C-21. In this case, unlike those in which those positions are occupied by halogen, the possibility exists that these are in fact prodrugs. That is, the compounds may have no intrinsic biological activity but need to be hydroxylated to the active entities in vivo. The synthetic sequence starts by formation of the bisketal 303 from $ll\alpha$ -acetoxy progesterone (302). Epoxidation affords predominantly the 5α , 6α -oxide (304). Reaction with methylmagnesium bromide both opens the oxiran and cleaves the ester (305). Successive treatment with aqueous acid and base serves to hydrolyze the ketal groups and dehydrate the resulting β -hydroxyketone (306). The α , β -unsaturated function provides a means for epimerization of the 6β -methyl group to 6α . There now remains the task of inverting the configuration at C-11 as well. Oxidation proceeds in















straightforward manner to give the ll-ketone (307); the highly hindered nature of the llketone permits selective ketal formation at C-3 and C-20 (308). Reduction by means of lithium aluminum hydride (309), followed by hydrolysis of the ketal groups affords antiinflammatory steroid medrysone (310).⁸⁸ The analogue containing additional unsaturation at C-1, endrysone (311), can presumably be obtained from 310 by any one of the standard dehydrogenation schemes.

REFERENCES

- 1. Y. Lefebvre, U. S. Patent 3,428,627 (1969).
- V. Prelog, L. Ruzicka and P. Wieland, Helv. Chim. Acta, 27, 250 (1944).
- 3. J. De Visser, Dutch Patent 95,275 (1960).
- 4. R. E. Brown, D. M. Lustgarten, R. J. Stanaback,
 M. W. Osborne and R. I. Meltzer, J. Med. Chem.,
 7, 232 (1964).
- 5. R. Clarkson, J. Chem. Soc., 4900 (1965).
- 6. Anon., Belgian Patent 647,699 (1964).
- See D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 164 (1975).
- 8. F. B. Colton, U. S. Patent 2,843,608 (1958).
- 9. R. T. Rapala, Belgian Patent 666,469 (1966); Chem. Abstr., 65: 5506h (1966).
- J. C. Babcock and J. A. Campbell, Belgian Patent 610,385 (1962); Chem. Abstr., 57: 13834 (1962).
- 11. M. S. de Winter, C. M. Siegmann and S. A.
Szpilfogel, Chem. Ind., 905 (1959).

- 12. Anon., British Patent 841,411 (1960).
- See D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 165 (1975).
- 14. J. Fried and T. S. Bry, U. S. Patent 3,096,353 (1963).
- H. L. Dryden, Jr., G. N. Webber and J. Wieczorek, J. Am. Chem. Soc., 86, 742 (1964).
- 16. P. Wieland and G. Anner, Helv. Chim. Acta., 50, 289 (1967).
- 17. Anon., Dutch Patent 6,406,797 (1965); Chem. Abstr., 64: 12759b (1966).
- D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 177 (1975).
- 19. J. S. Baran, J. Med. Chem., 10, 1188 (1967).
- 20. J. S. Baran, H. D. Lennon, S. E. Mares and E. F. Nutting, Experientia, 26, 762 (1970).
- H. Smith, G. A. Hughes, G. H. Douglas, G. R. Wendt, G. C. Buzby, Jr., R. A. Edren, J. Fisher, T. Foell, G. Gadstry, D. Hartley, D. Herst, A. B. A. Jansen, K. Ledig, B. J. McLoughlin, J. McMenamin, T. W. Pattison, P. C. Phillips, R. Rees, J. Siddall, J. Sinda, L. L. Smith, J. Tokolics and D. H. P. Watson, J. Chem. Soc., 4472 (1964).
- 22. D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 168 (1975).
- 23. Anon., British Patent 1,123,104 (1968); Chem. Abstr., 70: 4410b (1969).
- 24. D. Lednicer and L. A. Mitscher, Organic

- A. Popper, K. Prezewowsky, R. Wiechert, H. Gibian and G. Raspe, Arzneimittelforsh., 19, 352 (1969).
- C. Meystre, H. Frey, W. Voserand and A. Wettstein, Helv. Chim. Acta, 39, 734 (1956).
- 27. Anon., Belgian Patent 623,277 (1963).
- A. Ercoli, R. Gardi and R. Vitali, Chem. Ind., 1284 (1962).
- 29. J. C. Babcock and J. A. Campbell, U. S. Patent 3,341,557 (1967).
- 30. R. E. Counsell, P. D. Klimstra and F. B. Colton, J. Org. Chem., 27, 248 (1962); R. Mauli, J. H. Ringold and C. Djerassi, J. Am. Chem. Soc., 82, 5494 (1960).
- F. Sorm and H. Dykova, Coll. Czech. Chem. Commun., 13, 407 (1946).
- J. Joska, J. Fakjos and F. Sorm, Chem. Ind., 1665 (1958).
- 33. A. J. Manson, F.W. Stonner, H. C. Neumann, R. G. Christiansen, R. L. Clarke, J. H. Ackerman, D. F. Page, J. W. Dean, D. K. Phillips, G. O. Potts, A. Arnold, A. L. Beyler and R. O. Clinton, J. Med. Chem., 6, 1 (1963).
- 34. H. C. Neumann, G. O. Potts, W. T. Ryan and F. W. Stonner, J. Med. Chem., 13, 948 (1970).
- 35. F. W. Stoner, S. African Patent 68 04,986 (1969); Chem.
- 36. J. M. Nascimento and M. H. Venda, Rev. Port. Farm., 13, 472 (1963); Chem. Abstr., 61: 3163a (1964).

- 37. R. E. Counsell, P. D. Klimstra and R. E. Ranney, J. Med. Chem., 5, 1224 (1962).
- 38. W. R. Buckett, C. L. Hewett and D. S. Savage, Chim. Ther., 2, 186 (1967).
- 39. See D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 181 (1975).
- 40. Anon., Belgian Patent 624,370 (1963); Chem. Abstr., 60: 10764g (1964).
- 41. See D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 181 (1975).
- 42. Anon., Belgian Patent 646,957 (1964).
- 43. H. J. Ringold, E. Batres, A. Bowers, J. Edwards and J. Zderic, J. Am. Chem. Soc., 81, 3485 (1959).
- 44. See D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 179 (1975).
- 45. R. Wiechert, E. Kaspar and M. Schenck, German Patent 1,072,991 (1960).
- 46. R. Wiechert, U. S. Patent 3,234,093 (1966).
- 47. Anon., British Patent 1,095,958 (1967); Chem. Abstr., 69: 27645a (1968).
- 48. H. Grieś and J. Hader, German Patent 1,286,039 (1969); Chem. Abstr., 70: 88115v (1969).
- 49. See D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 200 (1975).
- 50. Anon., Belgian Patent 621,981 (1963).

- 51. R. T. Rapala and M. J. Murray, Jr., J. Med. Chem., 5, 1049 (1962).
- 52. G. Cooley, B. Ellis, F. Hartly and V. Petrow, J. Chem. Soc., 4373 (1955).
- 53. J. Fried, E. F. Sabo, P. Grabowich, L. J. Lerner,
 W. W. Kessler, D. M. Brennan and A. Borman, Chem. Ind., 465 (1961).
- 54. P. L. Julian and W. J. Karpel, J. Am. Chem. Soc., 72, 362 (1950).
- 55. J. S. Mills, O. Candiani and C. Djerassi, J. Org. Chem., 25, 1056 (1960).
- 56. See D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 207 (1975).
- 57. Anon., Belgian Patent 730,163 (1969).
- 58. R. M. Weier and L. M. Hoffman, J. Med. Chem., 18, 817 (1975).
- 59. See D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 192 (1975).
- R. Gardi, R. Vitali and A. Ercoli, *Tet. Lett.* 448 (1961).
- 61a. W. S. Allen and S. Bernstein, J. Am. Chem. Soc., 78, 1909 (1956).
- 6lb. S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, K. I. Feldman and R. H. Blank, J. Am. Chem. Soc., 81, 1689 (1959).
- S. Bernstein, R. Littell, J. J. Brown and I. Ringler, J. Am. Chem. Soc., 81, 4573 (1959).

- 63. J. A. Hogg and G. B. Spero, U. S. Patent 2,841,600 (1958); Organic Chemistry of Drug Synthesis, Vol. I, p. 195 (1975).
- 64. H. J. Ringold, J. A. Zderic, C. Djerassi and A. Bowers, German Patent 1,131,213 (1962); Chem. Abstr., 58: 10281c (1963).
- 65. Anon., British Patent 933,867 (1963).
- 66. Anon., French Patent 1,271,981 (1962); Chem. Abstr., 58: 11448a (1963).
- 67. See D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 180 (1975).
- 68. R. M. Dodson and C. Bergstrom, U. S. Patent 2,705,711 (1955); Chem. Abstr., 50: 5045f (1956).
- C. Bergstrom, R. T. Nicholson, R. L. Elton and
 R. M. Dodson, J. Am. Chem. Soc., 81, 4432 (1959).
- 70. See D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 193 (1975).
- 71. E. J. Agnello, S. K. Figdor, G. M. K. Hughes,
 H. W. Ordway, R. Pinson, Jr., B. M. Bloom and
 G. D. Laubach, J. Org. Chem., 28, 1531 (1963).
- 72. See D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 201 (1975).
- 73. J. Fried, A. Borman, W. B. Kessler, P. Grabowich and E. F. Sabo, J. Am. Chem. Soc., 80, 2339 (1958).
- 74. J. Fried, U. S. Patent 3,053,836 (1962).
- 75. L. T. Difazio and M. A. Augustine, German Patent 2,355,710 (1974); Chem. Abstr., 81: 91807e (1974).

- 76. S. Bernstein, J. J. Brown, L. I. Friedman and N. E. Rigler, J. Am. Chem. Soc., 81, 4956 (1959).
- 77. G. Baldratti, B. Camerino, A. Consonni, F. Facciano, F. Mancini, U. Pallini, B. Pateli, R. Sciaky, G. K. Suchowsky and F. Tani, *Experientia*, 22, 468 (1966).
- 78. H. J. Fried, H. Mrozik, G. E. Arth, T. S. Bry,
 N. G. Steinberg, M. Tishler, R. Hirschmann and S.
 L. Steelman, J. Am. Chem. Soc., 85, 236 (1963).
- 79. A. Ercoli and R. Gardi, S. African Patent 68 03,686 (1968).
- 80. For preparation of the corresponding 16-methyl analogue, see D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 205 (1975).
- J. A. Campbell, J. C. Babcock and J. A. Hogg,
 U. S. Patent 2,876,219 (1959).
- E. Kaspar and R. Phillippson, U. S. Patent 3,729,495 (1973).
- 83. R. M. Scribner, U. S. Patent 3,767,684 (1973).
- 84. See D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 202 (1975).
- 85. A.Bowers, U. S. Patent 3,201,391 (1965). 86. J. H. Fried, German Patent 1,917,082 (1969); Chem. Abstr., 72: 67206b (1970).
- 87. J. H. Fried, S. African Patent 68 00,282 (1968); Chem. Abstr., 70: 58146p (1969).
- G. B. Spero and J. L. Thompson, U. S. Patent 2,968,655 (1961).

7

Polycyclic Aromatic and Hydroaromatic Compounds

The ring systems covered in this chapter provide the molecular framework upon which the necessary functionality for a diverse range of pharmacologically active Intrinsic agonist activity is agents are assembled. rarely, if ever, attributable to the ring system itself among this class, but often replacement or "simplification" by omission of rings leads to a serious decrease in activity. This is generally considered to be due to a considerable alteration in lipid/water solubility ratio, a deleterious alteration in the spatial arrangement of the functions necessary to fire the receptor, a change in the pK such that altered intracellular concentrations are achieved, or some such factor. This lack of intrinsic pharmacophoric action is demonstrated clearly by the indanes in the first section. Of the six substances covered, each has a different main pharmacological action!

1. INDANES AND INDENES

Of a series of indanylthiocarbamates, tolindate (2) had significant antifungal properties. It is prepared simply from 5-indanyl thionochloroformate (1) by reaction with <u>N</u>-methyl-<u>m</u>-toluidine.¹ It presumably joins the fairly large family of organic compounds having sulfur divalently bound to carbon which are useful topical agents for dermatophytes.



When indan-2-one (3) forms a Schiff's base with aniline and this is reduced with sodium borohydride, the aminoindane 4 is found. The acidic hydrogen is removed with sodium hydride and this is in turn reacted with 3-diethylaminopropyl chloride to complete the synthesis of *aprindine* (5), an antiarrythmic agent.²



When 1-phenylindene (6) is treated successively with n-butyl lithium and dimethyl β -chloroethylamine, *indriline* (7), a central stimulant, is formed along with inactive isomer 8, both presumably arising via reaction with the intermediate aziridinium ion.³



Reaction of p-fluorobenzyl chloride with the anion of diethylmethylmalonate ester followed by saponification and decarboxylation leads to acid 9. Polyphosphoric acid cyclization leads to indanone 10. A Reformatsky reaction with zinc amalgam and bromoacetic ester leads to carbinol 11 which is then



dehydrated with tosic acid to indene 12. The active methylene group of 12 is condensed with p-thiomethylbenzaldehyde, using sodium methoxide as catalyst, and then saponified to give \underline{Z} -isomer 13 which is in turn oxidized with sodium metaperiodate to sulfoxide 14, the antiinflammatory agent sulindac.⁴

Phenyl indandiones with an acidic hydrogen often interfere with clot formation. When electron withdrawing groups are present in the p-position, acidity is increased and activity goes up. The opposite effect is seen with electron-donating substituents. Synthesized in the usual way, the anticoagulant bromindione (15) results from sodium acetate-catalyzed condensation of phthalic anhydride and p- α -bromophenylacetic acid.⁵



An analgesic compound that does not completely embody the essential structural features of the classical morphine rule is *dimefadane* (19). Friedel-Crafts alkylation of benzene with cinnamic acid using a Lewis acid catalyst gives β , β -diphenylacetic acid (16), which is cyclized to indanone 17. Heating with ammonium formate (Leuckart reaction) produces indanylamine 18 in a more efficient manner than does hydrogenation of the oxime. Heating with formaldehydeformic acid (Eschweiler-Clark reaction) then produces *dimefadane* (19),⁶ an analgesic with about the same potency as codeine but without much of the untoward gastrointestinal side effects of the natural product.



2. NAPHTHALENES

An analogue of tolindate (2) which has had greater success as an antifungal drug is tolnaftate (20). The synthesis follows the usual path, condensing β -naphthol with Cl₂CS and then reacting the resulting chlorothioformate with N-methyl-m-toluidine.⁷

It will be recalled that certain local anesthetic amides, such as *procainamide* and *lidocaine*, are active antiarrythmic agents. Annelation of a second aromatic ring is consistent with bioactivity. *Bunaftine* (21) is such an agent, prepared simply from reaction of the acid chloride of 1-naphthoic acid and β -dimethylaminoethylbutylamine.⁷



Interestingly, when propranolol is quaternized with methyl chloride, it loses its β -blocker activity and becomes the antiarrythmic agent pranolium chloride (22).⁸

A number of amidines have anthelmintic activity. Bunamidine (25), indicated for treatment of human pinworm infestations, is prepared from α -naphthylhexylether (23) by Friedel-Crafts type reaction with cyanogen bromide and aluminum chloride to give nitrile (24). This, then, is reacted with the magnesium bromide salt of di-<u>n</u>-propylamine leading to the naphthamidine structure (25).⁹-



Muscle relaxant activity is found in the aminoxymethylnaphthalene structure of *nafomine* (27). The synthesis proceeds from 1-chloromethyl-2-methylnaphthalene (26), which is reacted with <u>N</u>-carbethoxyhydroxylamine and base. In this way, the basic nitrogen is protected as the carbamate. Loss of the carbethoxy group either during reaction or on workup affords *nafomine* (27). 10 Certain ethanolamine analogues are active as CNS stimulants if they can be transported across the blood-brain barrier. One technique for bringing this about is to esterify them. One agent designed for this purpose, but which is more interesting as a vasodilator, is *nafronyl* (29).¹¹ The acid component is synthesized by condensing furfuryl chloride and methyl malonate followed by catalytic reduction, alkylation with 1-chloromethylnaphthalene and saponification/decarboxylation to give <u>28</u>.¹² Esterification with N,N-diethylethanolamine produces *nafronyl* (29).



A number of products in which one of the naphthalene rings has been reduced have interesting pharmacological properties. Reaction of tetralone <u>30</u> with dimethylamine under TiCl_4 catalysis produces the corresponding enamine (31). Reaction with formic acid at room temperature effects reduction of the eneamine double bond to product the tranquilizer and anti-Parkinsonian agent, *lometraline* (32).¹³.



Branched aryloxyacetic acids often have hypochloesterolemic activity. When tetralol <u>33</u> is reacted with phenol in a Friedel-Crafts reaction, α -tetralin derivative <u>34</u> is formed. This is reacted with ethyl α -bromoisobutyrate and saponified to produce the hypolipidemic agent, *nafenopin* (35).¹⁴



As noted above, phenylethanolamines are usually β -adrenergic agonists, whereas phenylpropanolamines show antagonist activity. A small series of phenyl-ethanolamine blockers is, however, known. When the haloatom of w-bromo-5,6,7,8-tetrahydro-2-acetonaphth-one (*36*) is displaced with isopropylamine and the

carbonyl group is reduced catalytically, the adrenergic blocking agent *bunitridine* (37) is produced.¹⁵



A number of tetralins with the appropriate side chains have β -adrenergic blocking activity. Presumably, the tetralin ring provides greater lipid solubility than the corresponding benzenes. *Bunolol (41)* is synthesized from phenolic tetralone (38) by sequential reaction with 2,3-dihydroxypropyl chloride (to <u>39</u>), tosyl chloride (to <u>40</u>), and t-butylamine to give *bunolol*.¹⁶ Restoration of a considerable amount of the water solubility of this small group of drugs is accomplised by incorporating a glycol moiety in the reduced ring. When 5,8-dihydronaphthol (42) is acetylated and then hydroxylated via the Woodward



modification of the Prevost process (silver acetate and iodine), glycol <u>43</u> is formed. The rest of the molecule is constructed in the usual way involving the sequence: saponification to the phenol, alkylation with epichlorohydrin, and displacement with <u>t</u>-butylamine to produce *nadolol* (44), a β -adrenergic blocking agent.¹⁷



Despite the best efforts of the World Health Organization, malaria remains a widespread tropical disease with substantial mortality. Of the many structural types explored in attempts to find prophylactic and chemotherapeutic agents, some have been naphthoquinones. During World War II, a large number of such guinones with aliphatic side chains were investigated. Several were active in ducks but not in man, and the reason for this difference was traced to man's ability to inactivate these materials by hydroxylation. To counter this, some agents with relatively very large hydrocarbon sidechains were For example, acylation of cyclohexanone enamine made. 45 with dihydrocinnamoyl chloride produced 46, which underwent ring-opening diketone cleavage with base to give acid 47. Wolff-Kishner reduction and hydrogenation



over a platinum catalyst produced saturated acid 48 that was converted to the acid chloride with $SOCl_2$ and then to the acyl peroxide (49) with H_2O_2 and pyridine. Heating 49 in acetic acid along with 2-hydroxynaphthoquinone resulted in radical formation and alkylation to produce the antimalarial agent, menoctone (50).¹⁸

FLUORENES

Many nonsteroidal antiinflammatory agents are acids and are believed to act by inhibiting prostaglandin synthesis. The synthesis of one such agent, *cicloprofen* (53), is illustrative. When fluorene 51 is acylated by ethyl oxalylchloride and AlCl₃, ketoester 52 results. Reaction with methyl Grignard reagent, acid dehydration of the tertiary carbinol, and catalytic reduction of the resulting terminal olefinic linkage produces the antiinflammatory agent, *cicloprofen* (53).¹⁹ Elements of the structure of *ibuprofen* and its congeners are clearly visible in *cicloprofen*.



A number of amines are also nonsteroidal antiinflammatory agents. One such agent was uncovered while searching for estrogenic substances. 9-Fluorenone (54) undergoes Grignard addition and dehydration with p-bromobenzylmagnesium bromide to give 55. Displacement of halogen with CuCN gives nitrile 56, which can be converted to the amidine in the usual way. Reaction with ethanol under acidcatalyzed anhydrous conditions leads to iminoether 57 which undergoes displacement with liquid ammonia to give the antiinflammatory agent, paranyline (58).²⁰



One substance intended to be an antiinflammatory agent has achieved much greater prominence because it

Polycyclic Aromatic Compounds

is an interferon inducer and is therefore protective against viral infections. This drug is *tilorone* (63).²¹ In its synthesis, fluorene (51) is sulfonated and converted to its potassium salt (59). This is oxidized with KMnO₄ to the fluorenone (60). Upon KOH fusion, nucleophilic substitution to the *bis*-phenol occurs, accompanied by ring cleavage, to give 61. Friedel-Crafts cyclization (ZnCl₂) restores the fluorenone system (62). Ether formation with β bromotriethylamine (probably via the aziridinium) produces *tilorone* (63).



4. ANTHRACENES

Anthracenes are planar by virtue of the necessity of maintaining aromaticity. When the central ring is reduced, an overall "butterfly" conformation is achieved. For reasons that are not yet understood at the molecular level, this conformation is often associated with central antidepressant activity.

The methylene group of anthrone 64 is acidic by virtue of doubly vinylic activation by the carbonyl group. Thus, treatment with methyl iodide and base leads to the 9,9-dimethyl derivative 65. Grignard reaction with δ -dimethylaminopropyl magnesium chloride gives tertiary carbinol 66 and subsequent acid dehydration produces melitracen (67), an antidepressant.²²



The same nonpolar conformation can be achieved by conversion to bicyclic structures. 1,4-Cycloaddition of ethylene to anthracene-9-carboxylic acid gives acid 68. Successive conversion to the Nmethylamide, via the acid chloride, followed by reduction with lithium aluminum hydride produced benzoctamine (69), a sedative and muscle relaxant.²³



Lengthening the side chain produces the antidepressant maprotiline (73), which has a topological relationship to the clinically useful tricyclic antidepressants. The requisite acid is constructed by conjugate addition of the carbanion of anthrone (64) to acrylonitrile, followed by hydrolysis to give 70. Reduction of the carbonyl group with zinc and ammonia gives anthracene 71 by dehydration of the intermediate alcohol function. Diels-Alder reaction with ethylene gives 72, which is converted to *maprotiline* $(73)^{23}$ by the same three-step sequence as used for *benzoctamine*.



5. DIBENZOCYCLOHEPTANES AND DIBENZOCYCLOHEPTENES Drugs in this structural class have effected a revolution in the treatment of severely depressed patients such that deinstitutionalization is a feasible public policy. The compounds often show other CNS activities which depend on the length of the side chain. Onecarbon chains generally lead to anticonvulsant activity; amines separated from the nucleus by three carbons usually ćonvey antidepressant activity. Selected examples possess significant anticholinergic activity.

Reaction of chlorodibenzocycloheptatriene 74 with butyl lithium, followed by carbonation produces acid 75, which is converted by ammonia, via the acid chloride, to *citenamid*e (76), an anticonvulsant.²⁴ The partially saturated analogue 77 is prepared

Polycyclic Aromatic Compounds

essentially the same way from chlorodibenzocycloheptadiene and is *cyheptamide*, also an anticonvulsant.²⁵ In the dihydro series the two benzene rings are not only out of plane, but also helical with respect to one another.



Base-catalyzed condensation between phenylacetic acid and phthalic acid produces enol lactone 78, which is reduced to benzoate 79 with HI and phosphorous. Friedel-Crafts cyclization by polyphosphoric acid followed by reduction produces alcohol 80. This alcohol forms ethers exceedingly easily, probably via the carbonium ion. Treatment with N-methyl-4--piperidinol in the presence of acid leads to the antidepressant hepzidine (81).²⁶



222

Polycyclic Aromatic Compounds

Inclusion of an acetylenic linkage as part of the side chain is apparently consistent with antidepressant activity. Reaction of propargyl magnesium bromide with dibenzocycloheptadieneone leads to carbinol 82. A Mannich reaction with formaldehyde and dimethylamine leads to 83 which, upon dehydration with SOCl₂ and pyridine, was transformed into *intriptyline* (84), an antidepressant.²⁷



Rigidity can be achieved with retention of the overall molecular conformation by use of a cyclopropyl ring in place of the olefinic bond bridging the two benzenes. Treatment of dibenzocycloheptatrieneone with dichlorocarbene generated from dichloroacetic ester and sodium ethoxide gives addition product 85. Reaction with cyclopropyl Grignard reagent gives carbinol 86 from which the gem-dihaloatoms are removed by lithium and <u>t</u>-butanol to give 87. Reaction of the latter with HCl generates chloride 88 via the intermediate cation (87a). Chloride displacement with methylamine completes the synthesis of antidepressant octriptyline (89).²⁸

Incorporation of the side chain amino group into a ring leads to tranquilizers. This is of special interest in that the amino group is now separated



from the tricyclic ring system by a smaller distance than is common to the other agents discussed. Reaction of amine 90 with δ -lactone 91 gives hydroxyamide 92. Cyclodehydration proceeds apparently through the expected Bischler-Napieralski intermediate 93 which cyclizes further to imine 94. Reduction with sodium borohydride or hydrogenation with platinum catalyst produces the undesired *cis* isomer. On the other hand, zinc and acetic acid reduction leads to the thermodynamically stable *trans* product, the minor tranguilizer *taclamine* (95).²⁹ The apparent conformation of *taclamine* is 96.

An alternate means of forming 96 arises from reaction of imine 97 with methylvinylketone in a variant of the Robinson annulation reaction. This



CH₂NH₂ (90)









can proceed in two directions, but 98 is the major product. Formation of the dithiolane derivative with $(CH_2SH)_2$ and BF_3 followed by Raney nickel desulfurization also leads to *taclamine*. The availability of ketone 98 makes it possible to prepare more highly functionalized derivatives. Addition, for example, of t-butyl lithium leads to tranquilizer *butaclamol* (99).³⁰ The large alkyl group is equatorial.



6. TETRACYCLINES

Still among the most frequently prescribed drugs, the antibiotic tetracyclines have decreased in popularity recently due to development of bacterial resistance in the clinic. The search for improved agents goes on.

When oxytetracycline (100) is reacted with <u>N</u>-chlorosuccinimide in dimethoxyethane, the active methine group at C_{11a} reacts and, apparently, there is formed a hemiketal bond between the C_6 -OH and the C_{12} -ketogroup (101). Dehydration with anhydrous HF of the tertiary, benzylic C_6 -OH group takes an exocyclic course, partially because aromatization to



the naphthalene system is forbidden by the presence of the blocking C_{11a} -chlorine atom. The product is sufficiently stable to allow electrophilic aromatic substitution. Reaction with N-chlorosuccinimide in liquid HF results in formation of the 7,lla-dichloro-6-methylene analógue (102). When the latter is subjected to chemical reduction (with sodium bisulfite, for example), the labile C_{11a} -Cl atom is removed and meclocycline (103) is formed. This broad spectrum antibiotic is about six times more potent in vitro against Klebsiella pneumoniae than methacycline itself.³¹ Nitro derivative 104 is an undesired side product in the synthesis of minocycline.³² Upon catalytic reduction it is converted to the corresponding aniline, amicycline (104). This substance is slightly less than half as active in vitro against Staphylococcus aureus than chlortetracycline (100), but is nearly twice as active as its C_7 isomer.^{33,34}



REFERENCES

- B. Elpern and J. B. Youlus, U. S. Patent 3,509,200 (1970); Chem. Abstr., 73: 14,546b (1970).
- P. Vanhoff and P. Clarebout, German Patent 2,060,721 (1971); Chem. Abstr., 75: 76,463x (1971).
- A. Kandel and P. M. Lish, Belgian Patent 667,739 (1966); Chem. Abstr., 65: 8,844c (1966).
- T. Y. Shen, B. E. Witzel, H. Jones, B. O. Linn and R. B. Greenwald, German Patent 2,039,426 (1971); Chem. Abstr., 74: 141,379x (1971).
- G. Cavallini, E. Milla, E. Grumelli and F. Ravenna, *Il Farmaco, Ed. Sci.*, 10, 710 (1955).

- J. A. Barltrop, R. M. Achison, P. G. Philpott, K. E. MacPhee and J. S. Hunt, J. Chem. Soc., 2928 (1956).
- T. Noguchi, Y. Hashimoto, K. Miyazaki and A. Kaji, Yakugaku Zasshi, 88, 335 (1968).
- M. Giannini, P. Boni, M. Fedi and G. Bonacchi, *Il Farmaco, Ed. Sci.*, 28, 429 (1973).
- 9. B. R. Luchesi, German Patent 2,333,965 (1974); Chem. Abstr., 80: 95,610n (1974).
- M. Harfenist, R. B. Burrows, R. Baltzly, E. Pederson, G. R. Hunt, S. Gurbaxani, J. E. D. Keeling and O. O. Standen, J. Med. Chem., 14, 97 (1971).
- 11. W. R. McGrath and E. M. Roberts, Belgian Patent 654,632 (1965); Chem. Abstr., 65: 669c (1966).
- E. Szarvasi, L. Neuvy and L. Fontaine, Compt. Rend., 260, 920 (1965).
- E. Szarvasi and L. Neuvy, Bull. Soc. Chim. Fr., 1343 (1962).
- 14. R. Sarges, German Patent 2,018,135 (1970); Chem. Abstr., 74: 22,601b (1971).
- 15. Anon., Dutch Patent 6,413,268 (1965); Chem. Abstr., 63: 13,178c (1965).
- 16. Anon., French Patent 1,390,056 (1965); Chem. Abstr., 62: 16,162d (1965).
- 17. E. J. Merrill, J. Pharm. Sci., 60, 1589 (1971).
- F. P. Hauck, C. M. Cimarusti and V. L.
 Narayanan, German Patent 2,258,995 (1973); Chem.
 Abstr., 79: 53,096y (1973).
- 19. L. F. Fieser, J. P. Schirmer, S. Archer, R. R.

Lorenz and P. Pfaffenbach, J. Med. Chem., 10, 513 (1967).

- 20. E. Stiller, P. A. Diassi, D. Gerschutz, D. Meikle, J. Moetz, P. A. Principe and S. D. Levine, J. Med. Chem., 15, 1029 (1972).
- 21. R. E. Allen, E. L. Schumann, W. C. Day and M. G. Van Campen Jr., J. Am. Chem. Soc., 80, 591 (1958).
- 22. E. R. Andrews, R. W. Fleming, J. M. Grisar, J. C. Kihm, D. L. Wenstrup and G. D. Mayer, J. Med. Chem., 17, 882 (1974).
- 23. T. Holm, Acta Chem. Scand., 17, 2437 (1963).
- 24. M. Wilhelm and P. Schmidt, Helv. Chim. Acta, 52, 1385 (1969).
- 25. M. A. Davis, S. O. Winthrop, R. A. Thomas, F. Herr, M.P. Charest and R. Gaudry, J. Med. Chem., 7, 88 (1964).
- 26. M. A. Davis, S. O. Winthrop, J. Stewart, F. A. Sunahara and F. Herr, J. Med. Chem., 6, 251 (1963).
- C. Van der Stelt, A. F. Harms and W. T. Nauta, J. Med. Chem., 4, 335 (1961).
- 28. J. F. Cavalla and A. C. White, British Patent 1,406,481 (1975); Chem. Abstr., 84: 4,744c (1976).
- 29. W. E. Coyne and J. W. Cusic, J. Med. Chem., 17, 72 (1974).
- 30. F. T. Bruderlein, L. G. Humber and K. Pelz, Can J. Chem., 52, 2119 (1974).
- 31. F. T. Bruderlein, L. G. Humber and K. Voith, J. Med. Chem., 18, 185 (1975).

- 32. R. K. Blackwood, J. J. Beereboom, H. H. Rennhard,
 M. Schach von Wittenau and C. R. Stephens, J.
 Am. Chem. Soc., 83, 2773 (1961).
- D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 215 (1977).
- 34. J. H. Boothe, J. J. Hlavka, J. P. Petisi and J.
 L. Spencer, J. Am. Chem. Soc., 82, 1253 (1960).
- 35. J. Petisi, J. L. Spencer, J. J. Hlavka and J. H. Boothe, J. Med. Chem., 5, 538 (1962).

8 Five-Membered Heterocycles

Heterocyclic compounds occupy a central position among those molecules that make life possible. In support, one need only mention the molecular basis of continuation of a given species, i.e., the heterocyclic purines and pyrimidines that form the building blocks of DNA and RNA. This realization, along with some early adventitious successes with heterocyclic drugs and the frequency with which the active principles of the important vegetable drugs of antiquity turned out to be heterocycles have led the medicinal chemist to devote a good deal of attention to this class of compounds as a source of potential thera-Perhaps as a result of this, somewhat peutic agents. over half the organic drugs to have been assigned generic names are heterocyclic molecules. It does not, however, follow that all biologically active molecules that contain a heterocyclic moiety owe 232

their activity to that fragment. As will be seen below, some classes of heterocycles do share a common biological response; in those cases it is of course a fair assumption that the heterocycle is a significant part of the pharmacophore. Cases are equally frequent, however, where it is apparent that the ring contributes little of a specific nature to the activity. A relatively neutral heterocyclic ring can often be substituted for a benzene ring with little qualitative effect on biological activity. For example, medicinal chemists often substitute a thiophene ring for a benzene ring in a drug. This practice is the venerable device of biological isosterism.

1. DERIVATIVES OF PYRROLE

Molecules whose sole heterocyclic moiety consists of a pyrrolidine ring are dealt with elsewhere in this book. There is a wealth of evidence to indicate that N-alkylpyrrolidine is usually a surrogate for a tertiary amine.

The large class of antiinflammatory phenylacetic acids are treated at some length in Chapter 4. A number of these agents consist of acetic or propionic acids substituted by an aroyl group. It is of interest that the central benzene ring of these molecules can be replaced by pyrrole with retention of activity. For example, Mannich reaction of N-methylpyrrole affords the corresponding dimethylaminomethyl derivative (2) and treatment with methyl iodide affords the quaternary salt (3). Displacement of the quaternary amine by means of cyanide leads to the substituted acetonitrile 4.¹ Friedel-Crafts acylation of that intermediate with the acid chloride from p-toluic acid gives a mixture of the 4-aryl ketone and the desired ketone 5. Hydrolysis with sodium hydroxide completes the synthesis of the antiinflammatory agent tolmetin (6).²





The wide latitude of structural variation consistent with bioactivity in this series is illustrated by the observation that antiinflammatory activity is maintained even when the second aromatic group is attached directly to the pyrrole nitrogen rather than to the heterocyclic ring via a carbonyl group as in the previous case. Condensation of pchloroaniline with hexane-2,5-dione (or its dimethoxytetrahydrofuran equivalent) affords pyrrole 7. The acetic acid side chain is then elaborated as above. Thus, Mannich reaction leads to the dimethylaminomethyl derivative 8, which is in turn methylated (9); the quaternary nitrogen replaced by cyanide to afford 10. Hydrolysis of the nitrile then gives *clopirac* (11).³



A change in both the substitution pattern and the oxidation state of the heterocyclic ring leads to a compound that exhibits antidepressant activity. This agent, cotinine (13), is found in nature as a product from the autoxidation of nicotine (12) (note the anagram). The compound can also be obtained in decidedly modest yield by oxidation of nicotine with hydrogen peroxide.⁴



A more highly substituted pyrrolidone, doxapram, shows activity as a respiratory stimulant. Preparation of this agent involves an interesting rearrangement, which in effect results in a ring exchange reaction. Alkylation of the anion from diphenylacetonitrile with the chloropyrrolidine 14 affords 15. Hydrolysis of the nitrile function leads to the



expected acid 16. Treatment of 16 with thionyl chloride presumably gives first the acid chloride 17; internal acylation would then lead to the bicyclic
quaternary ammonium salt 18. Attack on the two-carbon bridge by the gegenion would afford the observed chloroethyl pyrrolidone 19. (Regioselectivity may be due to the hindered environment about the one carbon bridge.) Displacement of chlorine by morpholine completes the synthesis of doxapram (20).⁵

The discovery of the sedative/hynoptic activity of derivatives of barbituric acid has led to very extensive dissections of that molecule. One outcome of this work is the realization that acylurea and acylamide derivatives often exhibit CNS depressant activity. A fair number of such molecules have been prepared that contain a succinimide or glutarimide pharmacophore. For example, Michael addition of cyanide to the stereochemically undefined cinnamate 21 affords intermediate 22. Acid hydrolysis leads directly to the tranquilizer fenimide (23).⁶ Although the stereochemistry of this compound is not specified, the fact that the ethyl group resides on an enolizable center makes it probable that this is in fact the thermodynamically more stable isomer.



2. DERIVATIVES OF FURAN

Many carbonyl derivatives of 5-nitrofurfural exhibit bacteriostatic activity. For example, the oxime, nifuroxime, has found some clinical use in the treatment of infections of the gastrointestinal and urinary tract. An impressive amount of work has been devoted to such derivatives in attempts to alter both their distribution and pharmacodynamics by modification of the substituents on the imine nitrogen. Much of this was detailed in the earlier volume. By way of additional examples, reaction of 5-nitrofurfural (24) with N-(2-hydroxyethyl)hydroxylamine gives the antimicrobial agent *nitrofuratrone* (25),⁷ probably the only nitrone to have been assigned a generic name. In a similar vein condensation with 2-ethylsemicarbazide leads to the semicarbazone *nitfursemizon*e (26),⁸ an antiprotozoal agent for use in poultry.



N-Aminoimidazolinones have found extensive use as synthons for such nitrofurans. Reaction of an appropriate 1,2-diamine (27, 31) with urea gives the desired heterocycle (28, 32). Nitrosation with nitrous acid, followed by reduction of the intermediate (29, 33) with zinc, gives the desired hydrazine (30, 34). Condensation of 30 with 24 affords *nifurdazil* (35).⁹ In a modification of the usual scheme, condensation of 34 with furfuraldehyde gives the hydrazone 36. Nitration of that intermediate affords *nifurimide* (37).¹⁰



It is of interest that antibacterial activity can be retained even when the imine carbon-nitrogen bond is replaced by a carbon to carbon double bond. Base-catalyzed condensation of 5-nitrofurfuraldehyde (24) with 2,6-dimethylpyridine (38) affords olefin 39. Treatment of this compound with hydrogen peroxide gives the corresponding N-oxide (40). Heating of that intermediate in acetic anhydride leads to acetoxylation of the 2-methyl group by the Polonovski reaction. Hydrolysis of the ester group affords *nifurpirinol* (42).¹¹



Taking the spacer ethylene moiety out and attaching a heterocyclic ring directly to the nitrofuran ring also results in an active antimicrobial agent. Condensation of bromoketone 43 (obtainable by halogenation of the corresponding acetylnitrofuran) with thiourea gives the aminothiazole 44. Although the detailed mechanism of this well known method for forming thiazoles is still under discussion, the reaction at least formally represents conversion of the ketone to an imine and displacement of the halogen by sulfur. Next, the primary amine is nitrosated

Five-Membered Heterocycles

(45), and this intermediate is reduced to the hydrazine (46). Acylation of the more basic terminal nitrogen with formic acid completes the synthesis of the antimicrobial agent *nifurthiazole* (47).¹²



Interposition of a phenyl ring between the furan and the nitro group radically changes the biological activity; product from this formal replacement is in fact a centrally acting muscle relaxant. In order to prepare the target lead, reaction of the diazonium salt (49) from p-nitroaniline (48) with furfural using cupric chloride as catalyst affords the coupling product 50. In a convergent synthesis, glycine derivative 51 is converted to the urea 52. Acidcatalyzed cyclization leads to aminohydantoin 53. Semicarbazone formation from aldehyde 50 with hydrazine derivative 53 affords dantrolene (54).



3. DERIVATIVES OF IMIDAZOLE

In its various oxidation states, the imidazole nucleus has proven to be an unusually fertile source of medicinal agents. Nitroimidazoles are very often associated with antimicrobial activity, whereas imidazolines are often present in drugs acting as adrenergic agents. These considerations suggest, as a working hypothesis, that these particular imidazole derivatives are integral parts of the respective pharmacophores. While nitrofurans are often prepared as antibacterial agents, nitroimidazole forms the basis for an extensive class of agents used in the treatment of infections by the protozoans. Unlike bacterial infections, protozoal infections are seldom life-threatening. The physical discomfort occasioned by such infections is, however, of sufficient importance to provide a useful therapeutic place for antiprotozoal agents. A particularly common set of such conditions are parasitic infections of the genitalia caused by *Trichomonas vaginalis*. These disorders are called trichomoniasis.

One of the problems complicating the chemistry of the imidazoles needed for preparing these agents is their structural ambiguity. Imidazoles undergo a facile tautomeric equilibrium involving a shift of the proton on nitrogen so that it is sometimes difficult to assign unambiguous structures to unsymmetrically substituted derivatives. Most drugs containing this ring system are alkylated on one of the ring nitrogens, which locks the molecule into a single tautomeric form and removes the source of ambiguity. The ambident character of imidazoles requires care in selecting those conditions that will lead to alkylation on the desired nitrogen atom.

By way of illustration, nitration of 2-isopropylimidazole (55) affords the 4- or 5-nitro derivative (56, 57). Alkylation with methyl iodide affords isomer 58. The same reaction carried out with dimethyl sulfate under neutral or acidic conditions provides the isomer methylated at the alternate nitrogen atom. There is thus obtained the antiprotozoal agent *ipronidazole* (59).¹⁴



In a similar vein, alkylation of 4-(5)-nitroimidazole with N-(2-chloroethyl)morpholine affords a mixture of N-alkylated imidazoles (61 and 62). The compound containing the adjacent ring substituents (61) is the antitrichomonal agent nimorazole.¹⁵



Acetylation of the hydroxymethyl imidazole 63 affords the corresponding ester (64), nitration (65) followed by hydrolysis gives intermediate 66, and reaction of this alcohol with potassium cyanate in hydrogen fluoride gives the carbamate ronidazole(67).¹⁶



Treatment of 2-methyl-4-(5)-nitroimidazole at reduced temperatures with N-benzoylaziridine in the presence of boron trifluoride etherate leads regiospecifically to the N-alkylated derivative (69). Hydrolysis of the amide function affords the primary amine 70. Acylation of this with methylchlorothioformate affords the antiprotozoal thioncarbamate, *carnidazole* (71).¹⁷ The same sequence, starting with the C-2 ethyl analogue (72) affords *sulnidazole* (75).¹⁷



Hydroxymethylation (formaldehyde) of nitroimidazole 76 affords 77, which is oxidized to aldehyde 78. To prepare the other fragment for this convergent synthesis, reaction of epichlorohydrin with morpholine leads to the aminoepoxide 79, which is reacted with hydrazine to afford 80. Reaction of this substituted hydrazine with dimethyl carbonate affords oxazolinone 81 by sequential ester interchange reactions. Condensation of 81 with aldehyde 78 affords the antitrichomonal agent moxnidazole (82).¹⁸

Nitroimidazoles substituted by an aromatic ring at the 2-position are also active as antitrichomonal agents. Reaction of p-fluorobenzonitrile (83) with saturated ethanolic hydrogen chloride affords iminoether 84. Condensation of that intermediate with the dimethyl acetal from 2-aminoacetaldehyde gives the imidazole 85. Nitration of that heterocycle with nitric acid in acetic anhydride gives 86. Alkylation with ethylene chlorohydrin, presumably under neutral conditions, completes the synthesis of the antitrichomonal, flunidazole (87).¹⁹





Imidazoles devoid of the nitro group no longer show useful antiprotozoal activity, however, several



such compounds have proven to be efficacious as antifungal agents. Alkylation of imidazole with bromoketone 89 prepared from 2,4-dichloroacetophenone (89) affords the displacement product 90. Reduction of the carbonyl group with sodium borohydride gives the corresponding alcohol 91. Alkylation of the alkoxide from that alcohol with 4-chlorobenzyl chloride leads to econazole $(92)^{20}$; alkylation with 2,4-dichlorobenzyl chloride gives miconazole (93).²⁰

Ethonam (99), an imidazole derivative with a very different substitution pattern, is also reported to possess antifungal activity. To prepare it, alkylation of aminotetralin 94 with methylchloroacetate gives the glycine derivative 95. Heating with formic acid then affords the amide 96; this compound is then reacted with ethyl formate to yield hydroxymethylene ester 97. Reaction with isothiocyanic acid gives the imidazole-2-thiol 98. (The



sequence may involve first hydrolysis of the formamido group, followed by addition of the amine to isothiocyanic acid; cyclization of the thiourea nitrogen with the formyl function would complete formation of the heterocycle.) Desulfurization by means of Raney nickel finishes the synthesis of ethonam (99).²¹

Not a hormone in the true sense of the word, histamine (100) does act as a potent mediator, leading to a host of biological responses. Many of the symptoms attributed to allergies owe their manifestations to exaggerated reaction to endogenous histamine released in response to an external stimulus. Secretion of gastric acid is another process under the control of histamine. It was hypothesized quite some time ago that pathological conditions traceable to excess histamine secretion or exaggerated sensitivity to that base could be treated by compounds that antagonized the response to histamine by competition for its receptor sites. The benzhydryl type antihistaminic compounds for the treatment of allergic diseases represent such competitive inhibitors.

It was noted, however, that a subset of responses known to be triggered by histamine failed to be blocked by the classical antihistaminic drugs. This, as well as further sophisticated pharmacological work, led to the classification of histamine receptors as H_1 and H_2 . To simplify grossly, the H_1 receptor controls the responses familiar to every hayfever sufferer; these effects can be alleviated readily by classicial antihistamines. The latter interestingly bear little or no structural similarity to histamine

250

itself. The H_2 receptor on the other hand controls secretion of acid in the stomach; classicial antihistamines have no effect on histamine-induced gastric acid secretion. Excess gastric acid secretion is believed by many to be intimately involved in the etiology of ulcers and exacerbation of preexisting ulcers; thus, compounds that can act as selective antagonists to the H_2 receptor are of considerable potential therapeutic significance.

The H₁ antagonists were developed serendipitously in the course of random screening. On the other hand, development of the H2 antagonists started from the premise that one of the best ways to produce an antagonist is to investigate compounds that bear some structural elements of the native agonists. Precedence for this came from comparison of the structure of β -adrenergic agonists and their blockers. Systematic modification of the histamine molecule achieved its first success toward the preparation of an H_2 antagonist with *burimamide* (107).²² Esterification of diamino acid 101 leads to 102. Reduction with sodium amalgam serves to convert the ester to a carbinol (103), and treatment of that aminoalcohol with ammonium isothiocyanate affords the imidazothione 105, probably by the intermediacy of thiourea 104. (Strict accounting of oxidation states seems to demand oxidation of the carbinol to an aldehyde in the course of this reaction.) Reduction of the thione with iron powder in acid probably proceeds via the enol form to afford the desired imidazole (106).²³ Condensation

with methyl isothiocyanate completes the synthesis of *burimamide* (107).



Further exploration of the histamine molecule revealed that addition of a methyl group to the 4-position led to an agonist with appreciably increased selectivity for the H_2 receptor.²⁴ Application of that principle to the prototype antagonist, as well as bioisosteric replacement of one of the side chain methylene groups by sulfur, affords metiamide (111).²⁵ Reduction of the imidazole carboxylic ester 108 gives the corresponding carbinol (109). Reaction of that with 2mercaptoethylamine, as its hydrochloride, leads to intermediate 110. In the strongly acid medium, the amine is completely protonated; this allows the thiol to express its nucleophilicity without competition and the acid also activates the alcoholic function toward displacement. Finally, condensation of the amine with methyl isothiocyanate gives metiamide (111). Side effects observed in some of the clinical trials with this agent were attributed to the presence of the thiourea function in the molecule. A systematic search for a functional group isoelectronic with thioureas revealed that cyanoguanides were biologically equivalent, and this substitution avoided the side effects of the former. In one of the schemes for preparing the desired product, primary amine 110 is reacted with complex nitrile 112. The resulting



addition-elimination sequence affords the highly successful agent for the treatment of ulcers, *cimetidine* (113).²⁵

Imidazole provides the nucleus for the antineoplastic agent *dacarbazine* (116). Diazotization of the commercially available aminoamide 114 with nitrous acid gives diazonium salt 115. Reaction of this salt with dimethylamine under anhydrous conditions leads to *dacarbazine* (116).²⁶



The diaryl indole, *indoxole* (117, see Chapter 11) represents a unique nonsteroidal antiinflammatory agent in that it lacks the labile acidic proton usually found in this class of drugs. Commercialization of indoxole was precluded by its marked photosensitizing side effect. Subsequent work from another laboratory showed that biological activity was retained when the indole nucleus was replaced by imidazole. Condensation of 4,4'-dimethoxybenzil with ammonium acetate and the ethyl hemiacetal of trifluoroacetaldehyde affords the aniinflammatory agent flumizole (120) in a single step.²⁷ The reaction can be rationalized by assuming either initial formation of a carbinolamine followed by condensation with one of the aryl carbonyls, or, alternately, by formation of an imine with one of the carbonyls followed by attack on the hemiacetal. Repetition of the process and tautomerization will lead to the imidazole ring.



(117)



(118)

The pharmacology of both the endogenous amines and drugs that act on the sympathetic nervous system can be best explained by assuming that responses are mediated by two different types of receptors. The existence of α - and β -adrenergic receptors has by now received considerable experimental backing. (It might be added as an aside that there is considerable evidence that these two classes of receptors can be further subdivided into β_1 and β_2 and possibly α_1 and α_2 receptors.) It is an interesting fact that with few exceptions, drugs that act on the β -adrenergic system all possess some chemical elements of the endogenous agonist epinephrine.

In contrast to this, there are no such structural constraints on α -adrenergic agonists or antagonists. Some of the most active α -sympathomimetic agents in fact contain an imidazoline moiety as part of the pharmacophore. The appropriate ring system can be

255

formed by a variety of methods. One of the more common involves condensation of a compound containing a carbon atom at the acid oxidation level (nitrile, imino ether) with ethylenediamine. Thus, reaction of the benzothiophenoacetonitrile derivative 121 with ethylenediamine gives the adrenergic α -agonist metizoline (122).²⁸ As expected the α -adrenergic activity of 122 is expressed as vasoconstriction. The compound is used topically as a nasal decongestant, acting on the mucosal vasculature.

In a similar vein, condensation of carboxylic acid 123 with ethylenediamine leads to domazoline (124).²⁹



Interposition of an oxygen atom between the aromatic ring and the imidazoline-bearing side chain leads to a compound reported to show antidepressant activity. Its preparation begins with alkylation of phenol 125 with chloroacetonitrile to afford intermediate 126. Condensation of that nitrile with the

256

mono-p-toluenesulfonamide from ethylenediamine affords the antidepressant imidazoline, fenmetozole (127).³⁰



Preparation of a rather more complex imidazoline drug starts with the alkylation of the carbanion from p-chlorophenylacetonitrile (128) with 2-bromopyridine. Reaction of the product (129) with ethylenediamine serves to form the imidazoline ring (130). Air oxidation then affords the tertiary carbinol by attack at the highly activated, multiply benzylic carbon. There is thus obtained the antidepressant dazadrol (131).³¹



Replacement of hydrogen by fluorine in biologically active compounds often leads to marked increases in potency. Although much work has gone into incorporation of fluorine in various drug series, compounds in which all the protons are replaced by that halogen atom are rare. One such relatively simple molecule in which only the active hydrogens remain shows sedative activity. Condensation of the imine from hexafluoroacetone (132) with sodium cyanide leads to a trimer which incorporates the cyanide (135). The sequence can be rationalized by assuming, as the first step, addition of cyanide to the imine function to form an aminonitrile (133). Reaction of the amine function with a second molecule of imine leads to the Cyclization, followed by reaction of the aminal 134. newly formed imine function with a third molecule of 133, gives the observed product as its sodium salt (135). Acidification (136), followed by hydrolytic



removal of the exocyclic aminal in strong acid, affords the sedative *midaflur* (137).³²

CNS activity apparently is retained when the heterocycle is changed to an imidazolidinone. Alkylation of the anion from the imidazolidinone 138 with dimethylaminoethyl chloride affords *imidoline* (139), ³³ a compound with tranquilizer activity.



The imidazole ring system provides the nucleus for two diuretic agents with structures unusual for that activity. Reaction of the N-cyanoaniline 140 (obtainable from the aniline (139) and cyanogen bromide) with N-methylchloroacetamide leads to the heterocycle 142. The sequence can be rationalized by



assuming N-alkylation of the aniline as the first step (141). Cyclization of that hypothetical intermediate gives azolimine (142).³⁴ The same sequence starting with p-chloroaniline (143) affords clazolimine (146).³⁴

Formal interchange of the carbonyl and imino groups and replacement of the methyl group by acetonitrile interestingly affords a compound with antiinflammatory and presumably no diuretic activity. Reaction of p-chlorophenylisocyanate (147, obtained from 143 and phosgene) with iminodiacetonitrile (148) gives the expected urea 149. Simple heating of that intermediate leads to condensation of the aniline with a nitrile group and formation of nimazone (150). 35,36 It is of interest that this agent is distantly related to the arylacetic acid antiinflammatory agent by a formal hydrolytic step.



Hydantoins are well-known anticonvulsant agents and as such have found extensive use in the treatment of epilepsy. Replacement of one of the carbonyl groups by thiocarbonyl is consistent with anticonvulsant activity. Thus, condensation of the ethyl ester of leucine (151) with allyl isothiocyanate gives the thiourea 152. Cyclization of that intermediate affords albutoin (153).³⁷



4. DERIVATIVES OF PYRAZOLE

Pyrazolones rank among some of the more venerable nonsteroidal antiinflammatory agents. The activity of antipyrine (154) was discovered not too long after that of aspirin. The preparation of a plethora of analogues of that compound, all bearing additional substitution at the 4-position, was described in some detail in the earlier volume.

The pyrazolone ring is apparently sufficiently nucleophilic to undergo Mannich reaction. Thus, condensation of *antipyrine* with formaldehyde and the substituted morpholine 155 affords directly the antiinflammatory agent morazone (156).³⁸ It is of interest that 155 has biological activity in its own right; this amphetamine derivative, phenmetrazine, not surprisingly, shows CNS stimulant and appetite-suppressing activity. $^{\mathbf{39}}$



Many of the modifications of the pyrazolone antiinflammatory agents are intended to increase the limited hydrophilicity of the parent molecules. Reaction of *aminopyrine* (157) with formaldehyde and sodium hydrogen sulfite affords *dipyrone* (158). The first step can be rationalized as an Eschweiler-Clark type N-methylation reaction, with bisulfite acting as the reducing agent. The resulting mono N-methyl analogue of 157 then apparently forms the sulfite adduct of the carbinolamine of formaldehyde.

5. DERIVATIVES OF OXAZOLE AND ISOXAZOLE As has been noted previously, the benzene ring of the phenylalkanoic acid antiinflammatory agents can be replaced by a variety of other aryl groups. However, each of these subclasses does seem to have its own specific SAR. In those cases where the aryl group is phenyl, optimal activity is obtained with a 2-arylated propionic acid; acetic acids are suitable for other classes. In the case at hand a terminally substituted propionic acid was chosen for further development. Acylation of aminoketone 159 with the half acid chloride-ethyl ester of succinic acid affords the amide 160. Cyclization by means of phosphorous oxychloride serves to form the oxazole ring. Saponification of the ester gives the antiinflammatory agent oxaprozin (162).⁴⁰



Amphetamine and its derivatives have been much used--and abused--as weight-reducing agents. As a consequence of the CNS-stimulating activity shown by

these agents, they are fairly efficient in suppressing symptoms of hunger. Much ingenuity has been exercised towards incorporating the phenylethylamine moiety in various molecules, in attempts to dissociate the anorexic activity of amphetamine from its other effects on the CNS. Never completely successful, this work has led to some molecules that look quite unlike the lead compound. In one study, reduction of the cyanohydrin from benzaldehyde (163) with lithium aluminum hydride affords the corresponding amino-Reaction of this intermediate with alcohol 164. cyanogen bromide in the presence of sodium acetate leads initially to the N-cyano intermediate 165. Acetate is a sufficiently strong base to catalyze the cyclization of the hydroxyl group onto the nitrile. The initially formed iminooxazolidine then rearranges to the more stable aminooxazoline (167) which is



known as aminorex (167).⁴¹ The same sequence starting from the cyanohydrins of p-chlorobenzaldehyde and p-trifluoromethylbenzaldehyde affords, respectively, $clominorex (172)^{41}$ and fluminorex (177).⁴¹

Formal oxidation of the methylene group in aminorex and dialkylation of the amine affords a compound with antidepressant activity. This activity is also not totally unexpected in a compound related, although very distantly, to amphetamine. Condensation of the alkoxide obtained from treatment of ethyl mandelate (178) with N,N-dimethylcyanamide can be envisioned to form initially the adduct 179. Cyclization of the anion onto the ester group then serves to form the oxazolinone ring. There is thus obtained the antidepressant thozalinone (180).⁴²



Phenylephrine (181) is a well-known α -sympathomimetic agent. As a consequence of this activity, the drug is used extensively for those conditions requiring a vasoconstricting agent. Modification of the functionality so as to include the aliphatic oxygen and basic nitrogen in an oxazolidine ring is compatible with this biological activity. Condensation of norphenylephrine (182) with cycloheptanone results in formation of the cyclic carbinolamine derivative ciclafrine (183). 43



Hydrazides of isonicotinic acid, *isoniazid* for example, were among the first compounds to be used as antidepressant drugs. It is generally accepted that these agents owe their action to increased brain levels of neurotransmitter amines by inhibition of the enzyme monoamine oxidase (MAO). The pyridine ring present in these molecules can, interestingly, be replaced by an isoxazole moiety. Thus, interchange of the isoxazole ester *184* with benzylhydrazine affords directly the MAO-inhibiting antidepressant *isocarboxazid* (*186*).⁴⁴



Five-Membered Heterocycles

6. DERIVATIVES OF THIAZOLE

The intensive research on β -adrenergic blocking agents has been discussed in some detail in Chapter As noted there, interposition of an oxymethylene 5. moiety between the aromatic ring and the aminoalcohol side chain of sympathomimetic agents is often compatible with antagonist activity. More recently it has been found that replacement of the aromatic ring in sympathomimetic amines or their antagonists by a heterocycle often gives active compounds (see also timolol, below). In the preparation of one example, displacement of halogen on 2-bromothiazole (187) by means of the alkoxide from glycerol acetonide (188) affords the ether 189. Hydrolysis of the acetonide leads to the glycol 190. Reaction with an equivalent of methanesulfonyl chloride gives the mesylate (191). (Although the terminal mesylate predominates, some secondary ester is probably formed as well; this is



not separated since it serves just as well for the subsequent reaction.) Exposure of the hydroxymesylate to sodium methoxide results in formation of the epoxide by internal displacement (192). Opening of the oxirane by means of isopropylamine affords finally $tazolo1 \ (193)$.⁴⁵ This compound, unexpectedly, does not show the properties of a classical β -adrenergic blocking agent; tazolo1 retains sufficient intrinsic sympathomimetic activity to be described as a cardiotonic agent.

As noted above, nitrofurans and nitroimidazoles have proven useful moieties for the preparation of antibacterial and antiprotozoal agents. It is thus of note that nitrothiazoles have also been used successfully in the preparation of antiparasitic agents. Condensation of 6-nitro-2-aminothiazole (194, available from nitration of aminothiazole) with ethylisocyanate yields the antiprotozoal agent nithiazole (195).⁴⁶ In a similar vein, condensation



268

of 194 with 2-chloroethylisocyanate leads to the chloroethylurea 196. Treatment with base serves to form the pendant imidazolinone ring. There is thus obtained the antischistosomal compound *niridazole* (197).⁴⁷

The thiazole ring has been found to be an occasional surrogate for a phenyl ring in certain antiinflammatory agents. Note that the side chain is restricted to a simple acetic acid in this series. Reaction of p-chloro-2-mercaptoacetophenone (198) with ethyl cyanoacetate in the presence of base affords thiazole 200. The reaction may involve an adduct such as the iminothioether 199 as an intermediate. Saponification of the ester moiety of 200 then gives the antiinflammatory agent fenclozic acid (201).⁴⁸



A distantly related acid with a more highly functionalized ring shows choleretic rather than antiinflammatory activity. That is, the compound is useful in those conditions in which the flow of bile is to be increased. Construction of the thiazolone ring is accomplished by a method analogous to that used above to build the thiazole ring. Thus, condensation of ethyl mercaptoacetate with ethyl cyanoacetate leads to the thiazolinone (203); an intermediate such as 202, involving addition of mercaptide to the nitrile function, can be reasonably invoked. Methylation of 203 with methyl sulfate proceeds on nitrogen with the concomitant shift of the double bond to give 204. Bromination of the active methylene (205) followed by displacement of halogen by piperidine affords the choleretic piprozolin (206). 49



7. MISCELLANEOUS FIVE-MEMBERED HETEROCYCLES Acylation with 3-chloropropionyl chloride of the

(206)

amidoxime 207 from 2-ethylphenylacetonitrile gives the corresponding N-acylated derivative 208. This cyclizes to the oxadizole (209) on heating. Displacement of chlorine with diethylamine affords the muscle relaxant-analgesic agent proxazole (210).⁵⁰



Thiadiazoles have proven of some utility as aromatic nuclei for medicinal agents. For example, the previous volume detailed the preparation of a series of "azolamide" diuretic agents based on this class of heterocycle. It is thus of note that the 1,2,5-thiadiazole ring provides the nucleus for a clinically useful agent for treatment of hypertension which operates by an entirely different mechanism, β -adrenergic blockade. In its preparation, reaction of the amide-nitrile 211 with sulfur monochloride leads directly to the substituted thiadiazole 212.⁵¹



Condensation of that intermediate with epichlorohydrin in the presence of a catalytic amount of piperidine affords the chlorohydrin 213, admixed with some epoxide. Reaction with tertiary butylamine completes construction of the propanolamine side chain. Displacement of the remaining halogen atom of 214 with morpholine under more strenuous conditions affords timolol (215).⁵²

A somewhat different scheme is used to gain entry to the alternate symmetrical 1,3,4-thiadiazole ring system. Reaction of thiosemicarbazide with isovaleric acid affords the ring system (217) in one step. The reaction may be rationalized by positing acylation to intermediate 216 as the first step. Sulfonylation of the amino group of 217 with pmethoxybenzenesulfonyl chloride affords the oral hypoglycemic agent *isobuzole* (218).⁵³ Careful examination of the structure will reveal elements of


the sulfonylurea functionality often associated with that activity.

REFERENCES

- W. Herz and J. L. Rogers, J. Am. Chem. Soc., 73, 4921 (1951).
- J. R. Carson, D. N. McKinstry and S. Wong, J. Med. Chem., 14, 646 (1971).
- 3. G. Lambelin, J. Roba, C. Gillet and N. P. Buu-Hoi, German Patent 2,261,965 (1973); Chem. Abstr., 79: 78604a (1973).
- W. G. Frankenburg and A. A. Vaitekunas, J. Am. Chem. soc., 79, 149 (1957).
- 5. C. D. Lunsford, A. D. Cale, Jr., J. W. Ward, B.

V. Franko and H. Jenkins, J. Med. Chem., 7, 302 (1964).

- C. L. Miller and R. A. Hall, U. S. Patent 3,183,245 (1965).
- Anon., British Patent 1,106,007 (1968); Chem. Abstr., 68: 86809e (1968).
- C. A. Johnson, U. S. Patent 3,253,987 (1966); Chem. Abstr., 65: 4332c (1966).
- F. F. Ebetino, British Patent 1,016,840 (1966); Chem. Abstr., 64: 11215c (1966).
- 10. J. G. Michels, U. S. Patent 2,927,110 (1960).
- 11. A. Fujita, M. Nakata, S. Minami and H. Takamatsu, Yakugaku Zasshi, 86, 1014 (1966).
- 12. W. R. Sherman and D. E. Dickson, J. Org. Chem., 27, 1351 (1962).
- H. R. Snyder, Jr., C. S. Davis, R. K. Bickerton and R. P. Halliday, J. Med. Chem., 10, 807 (1967).
- 14. K. Butler, H. L. Howes, J. E. Lynch and D. K. Pirie, J. Med. Chem., 10, 891 (1967).
- 15. P. N. Giraldi, V. Mariotti, G. Namini, G. P. Tosolini, E. Dradi, W. Logemann, I. de Carnevi and G. Monti, Arzneimittelforsch., 20, 52 (1970).
- 16. Anon., Netherlands Patent 6,609,552 (1967); Chem. Abstr., 67: 54123u (1967).
- 17. J. Heeres, J. H. Mostmans and R. Maes, German Patent 2,429,755 (1975); Chem. Abstr., 82: 156309m (1975).
- C. Rufer, H.J. Kessler and E. Schroder, J. Med. Chem., 14, 94 (1971).
- 19. Anon., Netherlands Patent 6,413,814 (1965); Chem. Abstr., 63: 18097b (1965).

- E. F. Godefroi, J. Heeres, J. Van Cutsem and
 P. A. J. Janssen, J. Med. Chem., 12, 784 (1969).
- 21. E. F. Godefroi, J. Van Cutsem, C. A. M. Van Der Eycken and P. A. J. Janssen, J. Med. Chem., 10, 1160 (1967).
- 22. J. W. Black, W. A. M. Duncan, C. J. Durant, C. R. Ganellin and E. M. Parsons, *Nature*, 236, 385 (1972).
- S. Akabori and T. Kaneko, J. Chem. Soc., Japan, 53, 207 (1932); Chem. Abstr., 27: 293 (1933).
- 24. G. J. Durant, J. C. Emmett, C. R. Ganellin, A.
 M. Roe and R. A. Slater, J. Med. Chem., 19, 923 (1976).
- 25. G. J. Durant, J. C. Emmett, C. R. Ganellin, P. D. Miles, M. E. Parsons, H. D. Prain and G. R. White, J. Med. Chem., 20, 901 (1977).
- Y. F. Shealy, C. A. Krauth and J. A. Montgomery, J. Org. Chem., 27, 2150 (1962).
- J. G. Lombardino, German Patent 2,155,558 (1972);
 Chem. Abstr., 77: 101607 (1972).
- Anon., French Patent M1614 (1963); Chem. Abstr.,
 58: 12574e (1964).
- 29. Anon., French Patent 1,353,049 (1964); Chem. Abstr., 61: 4146c (1964).
- 30. M. Julia, Bull. soc. Chim. Fr., 1365 (1956).
- 31. L. A. Walter, German Patent 1,905,353 (1969); Chem. Abstr., 72: 317904 (1970).
- 32. W. J. Middleton and W. J. Krespan, J. Org. Chem., 35, 1480 (1970).

- 33. W. B. Wright, Jr., and H. J. Brabander, Belgian Patent 623,942 (1962); Chem. Abstr., 60: 14513e (1964).
- 34. J. W. Hanifin, Jr., R. Z. Gussin and E. Cohen, German Patent 2,251,354 (1973); Chem. Abstr., 79: 18717e (1973).
- 35. F. K. Kirchner and A. W. Zalay, U. S. Patent 3,429,911 (1969); Chem. Abstr., 70: 96783b (1969).
- 36. J. Perronnet and J.P. Demonte, Bull. Soc. Chim. Fr., 1168 (1970).
- 37. S. Oba, Y. Koseki and K. Fukawa, J. Soc. Sci. Phot. Japan, 13, 33 (1951); Chem. Abstr., 46: 3885e (1952).
- 38. O. Hengen, H. Siemer and A. Doppstadt, Arzneimittelforsch., 8, 421 (1958).
- 39. F. H. Clarke, J. Org. Chem., 27, 3251 (1962).
- 40. Anon., French Patent 2,001,036 (1969); Chem. Abstr., 72: 66930w (1970).
- 41. G. I. Poos, J. R. Carson, J. D. Rosenau, A. P. Roszkowski, N. M. Kelley and J. McGowin, J. Med. Chem., 6, 266 (1963).
- R. A. Hardy, C. F. Howell and C. Q. Quinones,
 U. S. Patent 3,037,990 (1962).
- 43. G. Satzinger and M. Herrmann, German Patent 2,336,746 (1975); Chem. Abstr., 83: 10047 (1975).
- 44. T. S. Gardner, E. Wenis and J. Lee, J. Med. Chem., 2, 133 (1970).
- 45. A. P. Roszkowski, A. M. Strosberg, L. M. Miller, J. A. Edwards, B. Berkoz, G. S. Lewis, O. Halpern and J. H. Fried, *Experientia*, 28, 1336 (1972).

- 46. R. C. O'Neill, A. J. Basso and K. Pfister, U. S. Patent 2,755,285 (1956); Chem. Abstr., 51: 2873a (1957).
- 47. C. R. Lambert, M. Wilhelm, H. Striebel, F. Kradolfer and P. Schmidt, *Experientia*, 20, 452 (1964).
- 48. Anon., Netherlands Patent 6,614,130 (1967); Chem. Abstr., 68: 68976g (1968).
- 49. G. Satzinger, Ann., 665, 150 (1963).
- 50. Anon., British Patent 924,608 (1963); Chem. Abstr., 59: 6415h (1963).
- 51. L. M. Weinstock, P. Davis, B. Handelsman and R. Tull, Tetrahedron Lett., 1263 (1966).
- 52. B. K. Wasson, W. K. Gibson, R. S. Stuart, H. W. R. Williams and C. H. Yates, J. Med. Chem., 15, 651 (1972).
- 53. F. L. Chubb and J. Nissenbaum, Can. J. Chem., 37, 1121 (1959).

9 Six-Membered Ring Heterocycles

The six-membered ring heterocycles are of exceptional importance in the context of willingly self administered organic substances. One need only mention glucose and nicotine to make this point. The biological acceptability, within reasonable limits, of these materials is paralleled by the availability of a substantial number of drugs.

Substitution of a pyridine ring for a benzene ring often is compatible with retention of biological activity and occasionally this moiety is an essential part of the pharmacophore. Such substitution of =N for CH= is an example of the common medicinal chemical strategy known as bioisosterism.

1. PYRIDINES

The aliphatic hydrogens of α -picoline (1) are relatively acidic, so that treatment with phenyl lithium

Six-Membered Heterocycles

produces the carbanion which can add to chloral, forming 2. Acid hydrolysis leads to unsaturated acid 3, which is sequentially reduced to acid 4, Fischer-



esterified to 5 and transamidated to 6. Hofmann rearrangement with NaOBr followed by methanol gives carbamate 7, which is hydrolyzed to 8 and monomethylated. This fairly lengthy process affords the vasodilator, betahistine (9).¹

As the result of a screening program examining microbial fermentation products for pharmacological activity (other than antibiotic activity), fusaric acid (10) was isolated from Fusarium oxysporum following the discovery that extracts were potent inhibitors of dopamine β -hydroxylase, and thus interfered with the biosynthesis in vivo of the pressor neurohormone, norepinephrine. To refine this lead, amidation of 10 via the acid chloride was carried out to give the antihypertensive analogue *bupicomide* (11).²

Reaction of ethyl picolinate (12) with dimsyl sodium (from dimethylsulfoxide and sodium hydride) produces oxisuran (13), an antineoplastic agent.³



An adrenergic β_2 -receptor agonist related conceptually to salbutamol (14) can be made by substituting a pyridine ring for the benzene. In this case synthesis starts by hydroxymethylation and formation of the o-benzylether of 3-hydroxypyridine (15) to give Manganese dioxide perferentially oxidizes the 16. sterically more accessible primary alcohol group to the aldehyde, and subsequent aldol condensation with nitromethane produces nitrocarbinol 17. Catalvtic reduction with Raney nickel gives amine 18 which reacts in turn with t-butyl bromide to give amine 19. Hydrogenolysis of the protecting benzyl moiety finishes the synthesis of the bronchodilator, pirbuterol $(20).^{4}$

Substantial interest in the pharmacological properties of the nonsteroidal antiinflammatory agents related to *mefenamic* and *flufenamic* acid led to examination of a series of aminopyridines instead



of anthranilates. Thermal displacement of the halogen of 2-chloronicotinate derivatives (21) with the requisite anilines (22 or 23) led to antiinflammatory agents flunixin $(24)^5$ and clonixin (25),⁶ respectively.



The glyceryl ester of *clonixin*, *clonixeril (28)*, is also an antiinflammatory agent. It was prepared

via a somewhat roundabout method. *Clonixin* (25) was reacted with chloroacetonitrile and triethylamine to give 26. Heating 26 with potassium carbonate and glycerol acetonide displaced the activating group to produce ester 27 which was deblocked in acetic acid to produce *clonixeril*.⁷



Interestingly, a substance somewhat closely related to *flunixin*, *triflocin* (30), is a diuretic rather than an antiinflammatory agent. It can be prepared by nucleophilic aromatic displacement on 4-chloronicotinic acid (29) with <u>m</u>-trifluoromethyl-aniline.⁸

The topical antifungal agent *ciclopirox (32)* was formed from 2-pyrone *31* by an azaphilone reaction with hydroxylamine.⁹ This may be viewed at least formally as an ester (lactone)-amide exchange to an intermediate oximinoester, which ring-closes *via* an addition-elimination sequence to expel the original lactone ring oxygen in favor of the hydroxylamine nitrogen. Lactones which readily convert to lactams in this manner are known as azaphilones.



A 1,4-dihydropyridine having coronary vasodilatory activity and, therefore, intended for relief of the intense chest pains of angina pectoris is *nifedipine* (34). Using a portion of the classical Hantzsch pyridine synthesis, condensation of two moles of



ethyl acetoacetate and one each of ammonia and 2-nitrobenzaldehyde (collectively 33) leads to *nifedipine*.¹⁰ In the classical Hantzsch process, an oxidative step is needed to produce the pyridine ring system.

2. PIPERIDINES

Perhaps following up the rigid analogue concept, an epinephrine analogue with a cyclized side chain is the β_2 agonist/bronchodilator, *rimiterol (38)*. Reaction of 3,4-dimethoxybenzaldehyde (35) with 2-pyridyl lithium gives carbinol 36. Oxidation with permanganate and ether cleavage with HBr produces catechol 37. Hydrogenation with a palladium catalyst in acid medium leads to *rimiterol* by reduction of both the pyridine ring and the ketone function.¹¹





Propiophenone (39) does not easily form ketals directly. A solution for this difficulty involves conversion to the gem-dichloride (40) with PCl₅ and solvolysis to the ketal (41) using sodium methoxide. Acid-catalyzed ketal exchange with piperidine glycol 42 leads to the parenteral anesthetic, etoxadrol(43).¹² Repetition of the same steps starting with benzophenone led to dioxadrol (44), which is described as an antidepressant agent.¹²



In the course of an investigation aimed at refining hypotensive leads, 4-benzylpyridine (45) was reduced with a platinum catalyst in acidic medium to the corresponding piperidine, and this was alkylated with dimethylaminoethyl chloride to give 46. This



product, *pimetine*, is primarily of interest as a hypolipidemic agent.¹³

Possibly patterned after the clinically useful p-fluorobutyrophenone *haloperidol*, *lenperone (49)* too is a potentially useful tranquilizer. The synthesis proceeds from ketone 47 by alkylation with halide 48 followed by deketalization.¹⁴



The reader will recall that many sulfonylurea derivatives are oral hypoglycemic agents and therefore useful oral antidiabetic drugs in adult-onset diabetes. One more complex than most is *gliamilide* (54). Piperidine derivative 50, prepared by reduction of the corresponding pyridine, undergoes amide exchange to 51 on heating in pyridine with sulfamide $(H_2NSO_2NH_2)$. Reaction with hydrazine and HCl removes the phthaloyl protecting group, and acylation of the liberated amino function with 2-methoxynicotinyl chloride gave sulfonylurea 52. When this was reacted with the



bicyclic endo-diphenyl urea 53, amide exchange took place with expulsion of the better leaving group in this case, diphenylamine. There was thus obtained gliamilide (54).¹⁵



A number of years ago, pentamethylpiperidine 55 was found to be a rather potent, though not very specific, ganglionic blocking agent. This finding was of particular interest, as it was at that time believed that a quaternary ammonium function was a minimal structural feature for such drugs. In refining 55 as a lead, triacetone amine (56, synthesized from acetone, ammonia and calcium chloride) was reduced with sodium borohydride and N-alkylated to give 57. Cyanoethylation with acrylonitrile (with the aid of sodium t-butoxide) led to nitrile 58. Reduction with lithium aluminum hydride produced the primary amine and Eschweiler-Clark methylation (CH₂O and HCO₂H) completed the synthesis of *pemerid* (59), an antitussive agent.¹⁶ This activity is incidentally unrelated to ganglionic blockade.





Yet another (see *lenperone*) butyrophenone related to *haloperidol* is *pipamperone* (64). N-benzyl-4piperidone (60) has a venerable history as starting material for both central analgesics and CNS drugs. This synthon has been used by the Janssen group as a building block for numerous such drugs. Reaction of 60 with KCN and piperidine HCl, leads to the aminonitrile (61). The reaction probably represents cyanation of the intermediate imine. Hydrolysis with hot 90% sulfuric acid hydrates the nitrile to the carboxamide (62) and catalytic reduction deblocks the amine to give 63. Alkylation with p-fluorophenyl-3chloropropyl ketone using a catalytic amount of KI completes the synthesis.¹⁷





An interesting reaction ensues when the intermediate synthetic precursor (65) to synthon 60 is heated with phenylenediamine. The reaction can be rationalized as involving initial enamine-imine formation (66), followed by intramolecular attack on the ester carbonyl groups resulting in carbamate formation (67), which carbamate undergoes intramolecular transamidation to give urea 68. Other scenarios can be proposed and defended, but the net result is formation



of complex urea derivative 68, which readily undergoes catalytic reduction to 69, a versatile intermediate for the preparation of a variety of potential drugs. For example, alkylation with the requisite *haloperidol* fragment led to the tranquilizer, *benperidol* (70).¹⁸ Minor variants led to the tranquilizers oxiperomide (71),¹⁹ pimozide (72),²⁰ and clopimozide (73),²¹ and the analgesic, *benztriamide* (74).²²

Another fruitful investigation was based upon the cyanohydrin of ketone 60. This substance (75) undergoes hydride reduction to the corresponding aminoalcohol, which forms cyclic carbamate 76 on





heating with diethylcarbonate. Hydrogenolysis of the N-benzyl group and alkylation of the liberated amino group with phenethyl chloride gives *fenspiride* (77), an blocking bronchodilator.²³



Imidazolone analogues are available, for example, starting with piperidone 60 and reacting this with KCN and aniline followed by hydration to amide 78 in 90% sulfuric acid. Heating 78 with formamide results in the desired imidazolone formation (79). Catalytic hydrogenolysis (80) and suitable alkylation of this



secondary amine gives the tranquilizer, spiriline (81).²⁴ The closely related tranquilizers fluspiriline $(82)^{25}$ and fluspiperone (83) are made in the same general way.



When piperidone 60 is condensed with phenylacetonitrile, using sodium methoxide, 84 results. Catalytic reduction unexpectedly is nonselective, not only reducing the olefinic linkage, but also removing the benzyl protecting group. The product (85) has to be rebenzylated to 86 before cyanoethylation to 87 can be carried out. Hydrolysis of 87 with strong acid stopped at the glutarimide stage with the production of *benzetimide* (88), an orally active anticholinergic agent.²⁶



The action of phenyl Grignard reagent on piperidone 60 followed by dehydration and deblocking leads to intermediate \$9. When this is reacted with complex halide 90, fenpipalone (91), an antiinflammatory agent, results.²⁷ The requisite halide (90) is made by treatment of hydroxy pyrrolidine 94 with phosgene. The reaction may proceed via N-acylation to 93 which would undergo ring opening as shown with chloride ion to give 92, which would then cyclize as indicated to give 90. Such dealkylation of tertiary amines by acyl halides is a well-established reaction. An alternate and perhaps equally credible intermediate in this particular case would be bicyclo carbamate 95, which would be formed whether either O- or N-acylation were the first event.



A number of substituted β -aminoacetates inhibit the enzyme cholinesterase. The main function of this enzyme is to hydrolyze acetyl choline and thereby terminate the action of that substrate as a neurotransmitter. Such inhibition is functionally equivalent to the administration of exogenous acetylcholine. Direct administration of the neurotransmitter substance itself is not a useful therapeutic procedure due to rapid drug destruction and unacceptable side



effects. Aceclidine (100) was synthesized based upon these considerations. When glycine analogue 96 is catalytically reduced, cis-diester 97 is produced. Dieckmann condensation and saponification-decarboxylation then leads to bicyclopiperidone 98.²⁸ Borohydride reduction gives alcohol 99.²⁹ Acetylation completes the synthesis of aceclidine (100), a cholinergic agent.³⁰

Glutarimides may be regarded as oxidized piperidines, and many drugs containing this moiety are sedatives and anticonvulsants. A spiro derivative, *alonimid* (105) is such a sedative-hypnotic agent. It can be prepared by K t-butoxide catalyzed biscyanoethylation of phenylacetonitrile, leading to 101. Alkaline hydrolysis produces tricarboxylic acid <u>102</u> which is smoothly converted to the glutaric acid anhydride (103) with acetic anhydride. Friedel-Crafts cyclization leads to the 6-membered ring, with concomitant anhydride reorganization to give 104. The



azaphilone character of 104 is taken advantage of as reaction with ammonia produces the desired spiroimide 105.³¹ Interest in compounds of this generic type has cooled considerably in the wake of the *thalidomide* tragedy.

Homophthalimides have an active methylene group, and this property is retained by the octahydroisoquinoline derivative 106. Base-catalyzed benzylidine condensation with benzaldehyde gives tesimide (107), an antiinflammatory agent.³² The imine proton may be sufficiently acidic for this drug to be classed among the acidic nonsteroidal antiinflammatory agents.

As a means of introducing both rigidity and asymmetry for receptor discrimination, bicycloimides are potentially interesting pharmacological tools.



One such agent is prepared by NBS and peroxide bromination of ethyl 4-chlorophenylacetate (108) to give 109. This is converted by sodium hydride to the benzylic carbene, which is inserted into the double bond of ethyl acrylate to give *cis*-cyclopropane 110. Partial saponification cleaves the less hindered ester moiety to give 111. This is next converted to the alkoxyimide (112) on reaction with diethyl carbonate and diammonium phosphate. Stronger base (NaOEt) effects displacement to the imide (113), cyproximide, which has tranquilizing properties.³³



3. PIPERAZINES AND PYRAZINES

The classical synthetic method for constructing 2-aminopyrazines is illustrated by the synthesis of *ampyzine* (117), a CNS stimulant. Condensation of aminomalonamide and glyoxal leads to pyrazine 114. Hydrolysis to the acid and decarboxylation gives 2-hydroxypyrazine (115). Reaction with PCl₅ produces chloride 116, and heating with dimethylamine completes the synthesis of 117.³⁴



Methyl groups are introduced into the aromatic rings of pyrazines by varying the starting materials. For example, use of biacetyl and alanylamide produces trimethyl hydroxypyrazine *118*. Chlorination and thermal displacement with dimethylamine gives triampyzine (*119*), an anticholinergic agent intended to inhibit gastric secretion to control some kinds of peptic ulcer.³⁵



It has been discovered that direct chlorination of pyrazines can be accomplished and this has also been used to make candidate drugs. For example, when 2-methylpyrazine (120) is heated with chlorine in carbon tetrachloride, a mixture of the 3-chloro (121) and the 6-chloro derivatives result. After separation, 121 is heated with piperidine to give modaline (122), an antidepressant.³⁶



When piperazine (123) is reacted with two molar equivalents of 3-bromoacetyl chloride, the antineoplastic agent *pipobroman* (124) results.³⁷ This material is probably an alkylating agent. Exchange of the leaving groups by mesylate moieties is compatible with bioactivity. This has been accomplished by reaction of 124 with silver methanesulfonate to give *piposulfan* (125), also an antineoplastic agent.³⁸

$$\begin{pmatrix} H \\ N \\ H \\ H \\ H \\ (\underline{123}) \end{pmatrix} = BrcH_2CH_2CN NCCH_2CH_2Br CH_3SO_3CH_2CH_2CN NCCH_2CH_2OSO_2CH_3$$

Azaperone (128) is yet another of the tranquilizers related to haloperidol. Nucleophilic aromatic displacement of 2-chloropyridine by piperazine leads to amine 126 which is then alkylated in turn by 4-chloro-p-fluorobuterophenone (127) to give azaperone (128), which is said to be active by topical administration.³⁹



Alkylation of 1-(2-pyrimidyl)piperazine (129) with 3-chloro-1-cyanopropane gives nitrile 130, which is reduced with LAH and then acylated with spiro-glutaric anhydride 131 to synthesize the tranquilizer buspirone (132).⁴⁰



Alkylation of piperazine with the amide formed by reaction of chloroacetyl chloride with pyrrolidine gives amide 133. Acylation with 3,4,5-trimethoxycinnamoyl chloride completes the synthesis of the peripheral vasodilator, cinepazide (134).⁴¹



To round out this group of drugs in which the piperazine ring appears to serve primarily as a basic spacer unit, or a conformationally restricted ethylenediamine unit, reaction of N-phenylpiperazine (135) with acrylonitrile produces nitrile 136. Conversion



of the nitrile moiety to a tetrazole ring *via* a 1,3-dipolar addition process by sodium azide under ammonium chloride catalysis produces *zolterine* (*137*), an antihypertensive by virtue of its antiadrenergic/vasodilator activity.⁴² The tetrazole moiety is an

isoelectronic replacement for a carboxylic acid moeity in a number of drugs.

4. PYRIMIDINES

Two antibacterial agents related structurally to trimethoprim (138) are diaveridine (141) and ormetoprim (146). Diaveridine has been synthesized by a minor variant of the trimethoprim route⁴³ in which veratric aldehyde (139) is sequentially condensed with β -ethoxypropionitrile (to 140) and then guanidine to give 141.⁴⁴ Ormetoprim may be made analogously or



by benzylic bromination (NBS and peroxide) of acetylpyrimidine 142 to give 143, which alkylates 3,4-dimethoxytoluene to give substituted thymine 144 when treated with mercuric chloride in nitrobenzene. The amino groups are restored in the classic fashion by conversion of 144 to chloride 145 with POCl₃, and

Six-Membered Heterocycles

then displacement with ammonia to yield 146.⁴⁵ Ormetoprim (146) is a coccidiostat as well as an antibacterial agent.



Following the success of *pyrantel (147)* as an anthelmentic⁴⁶ a search was undertaken for an analogue that would have activity against adult whipworms as well. This effort was successful with the synthesis of tetrahydropyrimidine *150*, the anthelminitic, oxantel.⁴⁷ The C-methyl group of *149* is sufficiently activated that heating together with 3-hydroxybenz-aldehyde (*148*) in the presence of ethyl formate as a water scavenger produces oxantel directly.



Convulsive disorders are still a serious therapeutic problem and new agents are being actively sought. Classical therapy was based upon the barbiturates that are no longer in favor because of their many side effects and their suicide potential. Interestingly, a seemingly minor structural variation of phenobarbital (*151*, shown as its sodium salt) leads to an anticonvulsant of increased potency and which has less hypnotic activity. In this case, sodium phenobarbital serves as its own base (so the yield is limited to 50%) and reacts readily with chloromethylmethyl ether to produce *eterobarb* (*152*).⁴⁸



5. MISCELLANEOUS STRUCTURES

As befits their chemical heterogenecity, the miscellaneous group of drugs in this section belong to a wide range of pharmacological classes as well.

A pyridazine has found use as an antihypertensive agent. When levulinic acid is reacted with hydrazine, 153 results. This is aromatized to pyridazine 154 when reacted with bromine in acetic acid. One presumes a spontaneous dehydrobromination converts the intermediate to 154. Oxidation to the acid (155) is accomplished with potassium dichromate, and this is esterified to 156 under Fischer conditions. Conversion to chloro derivative 157 (with POCl₃) is followed by displacement with hydrazine to give 158. The synthesis of blood pressure-lowering hydracarbazine (159) is then completed by aminolysis with ammonia.⁴⁹



The triazinedione, triazuril (163) is active as a poultry coccidiostat. Diazonium salt 160, prepared from the appropriate aniline, is coupled with the active methylene group of N-carbethoxycyanoacetamide to give 161. Hydrolysis of the cyano group is accompanied by cyclization, and the resulting acid (162) is decarboxylated to triazuril (163) on heating.⁵⁰

A morpholine derivative is active as a muscle relaxant. To prepare it, reaction of arylphenethanolamine derivative *164* with sodium hydride and ethyl



chloroacetate leads to flumetramide (165).⁵¹

The carbonyl group of compounds related to 165 can be removed with retention of significant pharmacological activity. This can, of course, be done by lithium aluminum hydride reduction⁵² or by, in at least one significant case, reaction of aryloxyepoxide 166 with 2-aminoethylbisulfate to give the antidepressant agent, *viloxazine* (167).⁵³

The sultam, sulthiame (170), shows anticonvulsant activity. p-Aminobenzenesulfonamide can be alkylated by w-chlorobutylsulfonyl chloride (168) in



base via presumed intermediate 169, which spontaneously cyclizes to give sulthiame (170).⁵⁴



Reaction of 2,6-dimethylaniline with thiophosgene produces isothiocyanate *171*. When the latter is treated with 3-aminopropanol, thiourea *172* is formed, and this, when treated with hot concentrated hydro-chloric acid, cyclizes to *xylazine* (*173*), an analgetic and muscle relaxant.⁵⁵

A great many quaternary amines are active anticholinergic agents. One such parasympathetic blocking agent is made easily by reacting hyoscyamine with 4butoxybenzylbromide to produce *butropium bromid*e (174).⁵⁶



REFERENCES

- L. A. Walter, W. H. Hunt and R. J. Fosbinder, J. Am. Chem. Soc., 63, 2771 (1941).
- K. Shimizu, R. Ushijima and K. Sugiura, German Patent 2,217,084 (1972); Chem. Abstr., 78: 29778f (1973).
- 3. G. C. Morrison and J. Shavel, Jr., German Patent 1,955,682 (1970); Chem. Abstr., 73: 35225m (1970).
- W. E. Barth, German Patent 2,204,195 (1972); Chem. Abstr., 77: 151968n (1972).
- M. H. Sherlock, U. S. Patent 3,839,344 (1974); Chem. Abstr., 82: 16705n (1975).
- Anon., Dutch Patent 6,603,357 (1967); Chem. Abstr., 68: 59439g (1968).
- 7. M. H. Sherlock, South African Patent 68 02185 (1968); Chem. Abstr., 70: 96640c (1969); Swiss Patent 534,129 (1973); Chem. Abstr., 79: 18582g (1973).
- D. Evans, K. S. Hallwood, C. H. Cashin and H. Jackson, J. Med. Chem., 10, 428 (1967).
- 9. W. Dittmar, E. Druckrey and H. Urbach, J. Med. Chem., 17, 753 (1974); W. Dittmar and G. Lohaus, Arzneimittelforschung 23, 670 (1973); German Patent 2,214,608 (1973); Chem. Abstr., 79: 146419w (1973).
- 10. F. Bossert and W. Vater, South African Patent 68 01482 (1968); Chem. Abstr., 70: 96641d (1969).
- 11. G. H. Sankey and K. D. E. Whiting, J. Heterocycl. Chem., 9, 1049 (1972).
- W. R. Hardie, J. Hidalgo and I. F. Halvorstadt, J. Med. Chem., 9, 127 (1966).
- A. P. Gray, W. L. Archer, E. R. Spinner and C. J. Cavallito, J. Am. Chem. Soc., 79, 3805 (1957).
- 14. J. W. Ward and C. A. Leonard, French Patent 2,227,868 (1974); Chem. Abstr., 82: 170720v (1975).
- 15. R. Sarges, J. Med. Chem., 19, 695 (1976).
- 16. W. B. Lutz, S. Lazarus and R. I. Meltzer, J. Org. Chem., 27, 1695 (1962); N. P. Sanzari and J. F. Emele, U. S. Patent 3,755,586 (1973); Chem. Abstr., 80: 19550c (1974).

- 17. C. Van der Westeringh, P. Van Daele, B. Hermans,
 C. Van der Eycken, J. Boey and P. A. J. Janssen,
 J. Med. Chem., 7, 619 (1964).
- 18. Anon., Belgian Patent 626,307 (1963); Chem. Abstr., 60: 10690c (1964).
- 19. P. A. J. Janssen, U. S. Patent, 3,225,052 (1965); Chem. Abstr., 64: 8194b (1966).
- P. A. J. Janssen, W. Soudijn, I. Van Wijngaarden and A. Dreese, Arzneimittelforschung, 18, 282 (1968).
- 21. P. A. J. Janssen, C. J. E. Niemegeers, K. H. L. Schellekens, F. M. Lenaerts and A. Wanquier, Arzneimittelforschung, 25, 1287 (1975).
- 22. Anon., Belgian Patent 633,495 (1963); Chem. Abstr., 61: 1871c (1964).
- 23. Anon., Dutch Patent 6,504,602 (1965); Chem. Abstr., 64: 12679d (1966).
- 24. Anon., Belgian Patent 633,914 (1963); Chem. Abstr., 60: 15882d (1964).
- 25. P. A. J. Janssen, U. S. Patent 3,238,216 (1966); Chem. Abstr., 65: 8924d (1966).
- B. Hermans, P. Van Daele, C. Van der Westeringh,
 C. Van der Eycken, J. Boly, J. Dockx and P. A.
 J. Janssen, J. Med. Chem., 11, 797 (1968).
- 27. C. D. Lunsford and W. J. Welstead, South African Patent 67 03,192 (1968); Chem. Abstr., 70: 96,785d (1969).
- E. E. Mikhlina and M. V. Rubtsov, *Zhur. Obschei Khim*, 30, 163 (1960).
- L. H. Sternbach and S. Kaiser, J. Am. Chem. Soc., 74, 2215 (1952).

- C. A. Grob, A. Kaiser and E. Renk, Helv. Chim. Acta, 40, 2170 (1957).
- 31. G. N. Walker, U. S. Patent 3,379,731 (1968); Chem. Abstr., 69: 96497r (1968).
- 32. H. Zinnes, J. Shavel, Jr., N. A. Lindo and G. Di Pasquale, U. S. Patent 2,634,415 (1972); Chem. Abstr., 76: 72421e (1972).
- 33. E. N. Greenblatt and S. R. Safir, U. S. Patent 3,344,026 (1967); Chem. Abstr., 68: 29443m (1968).
- 34. G. W. H. Cheeseman, J. Chem. Soc., 242 (1960);
 F. H. Muehlmann and A. R. Day, J. Am. Chem. Soc., 78, 242 (1956).
- 35. Anon., British Patent 1,031,915 (1966); Chem. Abstr., 65: 5471g (1966).
- 36. W. B. Lutz, S. Lazarus, S. Klutchko and R. I. Meltzer, J. Org. Chem., 29, 415 (1964); M. Gainer, M. Kokorudz and W. A. Langdon, *ibid.*, 26, 2360 (1961).
- 37. S. Groszkowski, Roczniki Chem., 38, 229 (1964).
- 38. B. Horrom and J. A. Carbon, German Patent 1,177,162 (1964); Chem. Abstr., 61: 13329a (1964).
- 39. W. Sondijn and I. Van Wijngaarden, J. Labeled Compounds, 4, 159 (1968).
- 40. H. C. Ferguson, Y.H. Wu, J. W. Rayburn, L. E. Allen and J. W. Kissel, J. Med. Chem., 15, 477 (1972).
- 41. C. Fauran and M. Turin, Chim. Ther., 4, 290 (1969).

- 42. W. G. Stryker and S. Hayao, Belgian Patent 661,396 (1965); Chem. Abstr., 63: 18114e (1965).
- 43. D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 263 (1977).
- 44. P. Steinbuck, R. Baltzly and H. M. Hood, J. Org. Chem., 28, 1983 (1963).
- 45. Anon., Netherlands Application 6,514,743 (1966); Chem. Abstr., 65: 10598c (1966).
- 46. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 266267, Formula 94, (1977).
- 47. J. W. McFarland and H. L. Howes, Jr., J. Med. Chem., 15, 365 (1972).
- 48. C. M. Samour, J. F. Reinhard and J. A. Vida, J. Med. Chem., 14, 187 (1971).
- 49. D. Libermann and A. Rouaix, Bull. Soc. Chim. Fr., 1793 (1959).
- 50. M. W. Miller, German Patent 2,149,645 (1972); Chem. Abstr., 77: 164712z (1972).
- 51. W. F. Gannon and G. I. Poos, U. S. Patent 3,308,121 (1967); Chem. Abstr., 67: 32693c (1967).
- 52. K. B. Mallion, R. W. Turner and A. H. Todd, British Patent 1,138,405 (1969); Chem. Abstr., 70: 96804j (1969).
- 53. S. A. Lee, British Patent 1,260,886 (1972); Chem. Abstr., 76: 99684e (1972).
- 54. B. Helferich and R. Behnisch, U. S. Patent 2,916,489 (1959).
- O. Behner, H. Henecka, F. Hoffmeister, H. Kreiskott, W. Meiser, H. W. Schubert and W.

Wirth, Belgian Patent 634,552 (1964); Chem. Abstr., 61: 4369b (1964).

56. S. Tanaka and K. Hashimoto, German Patent 1,950,378 (1970); Chem. Abstr., 73: 98,819d (1970).

¹⁰ Compounds Related to Morphine

The development of the first effective analgesic drug, opium, was almost certainly adventitious, and occurred in prehistoric times. The use of the dried exudate from slitting the immature capsule of the opium poppy, *Papaver somniferum*, as an analgesic, sedative and euphoriant, has a long folkloric history. Isolation of the principal active component *morphine* (1) as a pure crystalline compound represented one of the early landmarks in organic chemistry.



 $(\underline{1})$

The history of this class of analgesics might have stopped there were it not for the manifold ancillary activities shown by that molecule. Although still one of the most widely used agents for treatment of severe pain, morphine is a drug that must be used with caution. Side effects include respiratory depression, induction of constipation, and sometimes marked sedation. The one property that most severely limits use of this drug is its propensity to induce physical dependence in patients subjected to more than casual exposure.

Compounds Derived from Morphine 1. Attempts to modify the molecule so as to maximize analgesic activity at the expense of side effects date back almost a full century. It is ironic that heroin (diacetyl morphine) was in fact prepared in the course of one such program. Although early efforts concentrated on modification of the natural product, the growth of synthetic organic chemistry has led more recently to the preparation of molecules that represent much more deep seated changes in structure. The concept of molecular dissection has been used widely in the design of such lead compounds. Some of the more recent molecules inspired by morphine do in fact show promise of providing analgesia with significantly reduced side effects so that compounds are now available that show a much reduced tendency to induce physical dependence, *i.e.*, addiction liability.

It has long been a puzzle to medicinal chemists

why a natural product that has no evolutionary association with Homo sapiens should show such profound biological activity. The puzzle was, if anything, intensified by reports of the occurrence of receptors for morphine and related opioids in mammalian brains. Receptors for various endogenous hormones and other chemical transmitters have been recognized for some time; it was, however, unexpected to find a specific receptor for an exogenous chemical that plays no known role in the normal biochemical functioning of a mammal.

The identification of the morphine receptor spurred an effort in many laboratories to find an endogenous agonist for which that receptor was normally intended.¹ Ultimately, a pair of pentapeptides that bound quite tightly to opiate receptors were isolated from mammalian brains. These peptides, called *enkephalins* (2, 3), show many of the activities of synthetic opiates in isolated organ systems. They do in fact show analgesic activity when injected directly into the brain. It is thought that lack of activity by other routes of administration is due to their rapid inactivation by peptide cleaving enzymes.

> HTyr-Gly-Gly-Phe-MetOH met-enkephalin (2) HTyr-Gly-Gly-Phe-LeuOH leu-enkephalin (3)

Fragments of the peptide hormone β -lipotropin have been found to show similar binding to opiate receptors. These molecules, the endorphins, show profound CNS activity in experimental animals. It is of interest that one of these, β -endorphin, incorporates in its chain the exact sequence of amino acids that constitutes methionine enkaphalin.

Although these findings are too recent to have had an impact on the design of analgesics, it has already been noted that when properly folded, molecular models of the enkaphalins show a good topographical correspondence with molecules such as morphine. Unless this topographic relationship is fortuitous, this has the most profound future implications for the rational design of analgesic drugs.

Morphine and related opiates are known to suppress the cough reflex; these compounds have thus been used extensively in antitussive preparations. Since this activity is not directly related to the analgesic potency, the ideal agent is one that has much reduced analgesic activity and thus, presumably, lower addiction potential. The weak analgesic codeine (4) is



still used in many such preparations, and a variety of analogues have been prepared as substitutes. For example, condensation of *dihydrocodeinone* (5) (available in several steps from 4) with hydroxylamine derivative 6 affords the antitussive agent *codoxime* (7).²

Replacement of the N-methyl group of morphine by an allyl moiety leads to a narcotic antagonist. That is, the resulting drug, *nalorphine*, not only shows little analgesic activity but will in fact block most of the actions of morphine. Presumably, it binds to the opiate receptor but has little intrinsic agonist activity. Incorporation of a new hydroxyl group at the 14-position in morphine has been found empirically to potentiate greatly the activity of morphine. Combination of these two modifications in a single drug gives a very potent narcotic antagonist, naloxone (8). It is possible, by suitable modification of various structural features in narcotic analgesic molecules, to devise compounds, which show both agonist and antagonist activities; it has been found both in experimental animals and in man that such mixed agonists-antagonists afford analgesics with much reduced addiction liability. The work that follows apparently was aimed at building agonist activity into the naloxone structure.

The starting material for these 14-hydroxy compounds is the opium alkaloid *thebaine* (9). Although present in only small amounts in the alkaloid fraction from *Papaver somniferum*, it constitutes the major component (as much as 26% of the dried latex) from a related poppy, Papaver bracteatum.³ Reaction of 9 with hydrogen peroxide leads to intermediate 11. The oxidation may be visualized as a 1,4-oxidation process of the diene system to afford an intermediate such as 10. Successive reduction of the double bond (12) and demethylation affords oxymorphone (13).⁴ This molecule is then protected as the diacetate; N-demethylation followed by saponification affords the key intermediate 14.⁵

Alkylation of the secondary amine in 14 with 1-bromo-3-methy1-2-butene leads to the mixed analgesic agonist-antagonist nalmexone (15).⁶ In a somewhat more elaborate scheme, the carbonyl group in 14 is first protected as its cyclic ethylene ketal (16). Alkylation with cyclopropylcarbonyl chloride affords the O,N-diacylated product (17); treatment with lithium aluminum hydride results in reductive cleavage of the O-acyl group and reduction of the amide carbonyl to a methylene group (19). Hydrolysis of the acetal then affords the mixed analgesic/antagonist naltrexone $(21)^{7}$ Acylation of 14 with cyclobutylcarbonyl chloride followed by the same series of transformations as above leads to intermediate 22. Reduction of the carbonyl group in that molecule with sodium borohydride gives the analgesic agonist/antagonist nalbuphine (23).7

An indication that the SAR of the narcotic antagonists was more complex than had been anticipated came from the observation of the tremendous increase in milligram potency obtained by fusing an additional bicyclic ring onto the basic morphine structure. The

















resulting molecule, **etorphine** (26) shows three orders of magnitude greater potency than morphine; this could be interpreted as a better or tighter fit to the receptor. Synthesis of this molecule also takes advantage of the diene function found in thebaine. Thus, Diels-Alder condensation of 9 with methyl vinyl ketone affords the bicyclic adduct 24. The new ring is formed by approach of the dienophile from the face containing the nitrogen bridge, since this is in fact the least hindered side of the molecule (9a). Reaction of the side chain ketone with propylmagnesium bromide then leads to intermediate 25; demethylation of the phenolic ether affords etorphine (26).⁸

In this series, too, replacement of the N-methyl by a group such as cyclopropylmethyl leads to a compound with reduced abuse potential by virtue of mixed agonist-antagonist action. To accomplish this, reduction of 24 followed by reaction with tertiary butylmagnesium chloride gives the tertiary carbinol 27. The N-methyl group is then removed by the classic von Braun procedure. Thus, reaction with cyanogen bromide leads to the N-cyano derivative (28); hydrolysis affords the secondary amine 29. (One of the more efficient demethylation procedures, such as reaction with ethyl chloroformate would presumably be used today.) Acylation with cyclopropylcarbonyl chloride then leads to the amide 30. Reduction with lithium aluminum hydride (31) followed by demethylation of the phenolic ether affords buprenorphine $(32).^{9}$



(<u>9a</u>)











2. Morphinans

In the course of earlier work it had been ascertained that the furan oxygen of morphine was not essential to analgesic activity.¹⁰ This observation led to the preparation of a considerable number of quite potent deoxy analogues of morphine, since these compounds were relatively easily accessible by totally synthetic routes. Combination of this deoxy nucleus (called morphinan) with the tertiary hydroxyl found in molecules such as naloxone has led to quite potent analgesics; appropriate modification of the substituent on nitrogen then has led to mixed agonistsantagonists. These compounds, too, show much reduced addiction liability. For example, alkylation of the anion from tetralone 33 with 1,4-dibromobutane gives the spiro ketone 34. Condensation of the carbonyl group with the anion obtained on treatment of acetonitrile with butyl lithium leads to the carbinol 35; the cyano group is then reduced to the primary amine (36) by means of lithium aluminum hydride. Treatment of 36 with acid leads to the corresponding tertiary benzylic carbonium ion; this undergoes Wagner-Meerwein rearrangement and proton loss to give the phenanthrene derivative 37, a key intermediate in this series.¹¹ Several schemes have been developed for proceeding from this point; however, some relatively direct routes suffer from lack of regiospecificity. For example, internal cyclization of epoxide 38 affords both the desired ring system (45) and its isomer $(39).^{12}$ In one regiospecific route, amine 37 is



treated with bromine to afford the bicyclic bromoamine 40. The reaction can be rationalized by assuming initial bromonium ion formation on the underside of the molecule; opening of the ring by the amine will lead to the observed product as its hydrobromide salt. Reaction of 40 with sodium bicarbonate results in the rearrangement to the desired skeleton. The inorganic base is not in this case the reagent; rather, it is likely that once 40 is present as the free base, it undergoes the internal displacement via the aziridinium ion. Following protection of the amine as the trifluoroacetamide (42), the double bond is oxidized to give mainly the β -epoxide (43). Hydrolysis of the amide linkage (44) followed by treatment with lithium aluminum hydride affords the desired aminoalcohol 45. Both the regio and stereochemistry of this last reaction follow from the diaxial opening of oxiranes. Acylation of this intermediate with cyclobutylcarbonyl chloride gives the corresponding amide (46). Reduction of the amide (47) followed by O-demethylation affords butorphanol (50).¹³ The same sequence on 45 starting with cyclopropyl carbonyl chloride leads to oxilorphan (51).¹⁴

3. Benzomorphans

Further dissection of the morphine molecule showed that potent analgesics could be obtained even when one of the carbocyclic rings was omitted. One such compound, *pentazocine* (52), has found considerable use as an analgesic in the clinic. There is considerable evidence to indicate this drug has much less

















addiction potential than does morphine. The corresponding cyclopropylmethyl analogue cyclazocine (53), perhaps as a consequence of its greater balance of antagonist activity, has proven to be quite hallucinogenic.

Omission of the phenolic group from cyclazocine results in a molecule which retains analgesic activity. In a classical application of the Grewe synthesis,¹⁵ the methylated pyridinium salt 54 is condensed with benzylmagnesium bromide. There is thus obtained the Treatment of that intermediate dihvdropvridine 55. with sodium borohydride results in reduction of the iminium function to afford the tetrahydro derivative Cyclization of 56 on treatment with acid leads 56. to the desired benzomorphan nucleus. The cis compound (57) is separated from the mixture of isomers and demethylated by the cyanogen bromide procedure (58, 59). Acylation with cyclopropylcarbonyl chloride (to 60) followed by reduction of the resulting amide yields volazocine (61).¹⁴

Oxidation of the benzylic methylene group in cyclazocine to a ketone is also consistent with analgesic activity. Acetylation of benzomorphan 62 affords the diacetate 63. Selective hydrolysis of the phenolic acetate (64) followed by methylation of the thus uncovered phenol affords intermediate 65. The remaining acetate is then hydrolyzed (66). Oxidation of that compound with chromium trioxide in sulfuric acid leads cleanly to the desired ketone (67). Treatment with hydrobromic acid serves to demethylate the phenolic ether function (68). Direct

alkylation of the secondary amine with cyclopropylmethyl bromide gives *ketazocine* (69).¹⁶



4. Phenylpiperidines

Extensive molecular dissection of the morphine molecule over the past several decades led to a host of molecules which showed narcotic analgesic activity even though they possessed but faint suggestion of the structural features present in morphine itself. Thus, both cyclic molecules such as meperidine (70) and alphaprodine (71), and acyclic compounds such as methadone (72) were found to be effective analgesics. Common features of these compounds were formalized by the Beckett-Casy rule, which states as minimal required structural features: (a) an aromatic ring attached to (b) a quaternary center, and finally (c) the presence of nitrogen at a distance equivalent to two carbon atoms from the quaternary center (73). Although sufficient exceptions have recently been found to suggest that this is an oversimplification, it is of historical importance because of its guiding influence on analgesic research over a considerable span of time.





It will be recalled that a common side effect of *morphine* is the induction of constipation. This property of the drug has often been exploited in the design of preparations used to control diarrhea.



There has also been some work devoted to the preparation of a compound that would show greater selectivity toward activity on the gut and away from activity over the CNS. *Diphenoxylate* $(74)^{17}$ has been used extensively in humans for just this purpose; although the drug shows some selectivity, it is far from free of narcotic effects. (The curious will note the compound follows the Beckett rule both in the piperidine and side chain moieties.) Treatment of 74 with potassium tertiary butoxide in DMSO results in saponification to the free acid *difenoxin* (75).¹⁸

Certain esters have often been employed in attempts to confer organ selectivity to molecules possessing carboxyl functions. Thus, for example, treatment of piperidinecarboxylic acid 76 with Nhydroxysuccinimide and DCC affords the ester 77. In a convergent synthesis, the anion from diphenylacetonitrile (78) is alkylated with dibromoethane to afford the bromide 79. Alkylation of the piperidine derivative 77 with that halide 79 gives the antidiarrheal agent *difenoximide* (80). The same sequence starting with the phenoxyethyl ester 81 gives fetoxylate (82).²⁰

Derivatives of 4-phenyl-4-hydroxypiperidine, which may be formally regarded as reversed meperidines, have yielded a series of potent antipsychotic drugs such as *haloperidol (83)* and *bromoperidol (84)*. Retention of carbon at the 4-position interestingly leads to a molecule with quite different activity. The starting material for this molecule could be synthesized by first preparing the amide (86) from the benzyl (85) derivative of meperidine. Reduction of the amide would then afford the primary amine (87). Acetylation (88) followed by removal of the benzyl group would afford the key intermediate (89). Alkylation with 4-chloro-p-fluorophenylbutyrophenone affords *aceperone* (90).²¹ This compound exhibits vasodilator and antihypertensive activity.



(90)

Alkylation of diphenylpiperidinols with bis(pfluorophenyl)butyl side chains has also led to antipsychotic compounds. For example, reductive cyclization of the acylation product (91) from fluorobenzene



and succinic anhydride gives the corresponding butyrolactone 92. Treatment with fluorobenzene in the presence of a Friedel-Crafts catalyst leads to the diarylated acid 93. The carboxyl group is then reduced to the corresponding carbinol 94 by means of lithium aluminum hydride, and this is converted to the chloro compound 95 with thionyl chloride. Alkylation of piperidine 96 with that halide gives the neuroleptic compound *penfluridol* (97).²²

The use of phenylpiperidinols rather than the meperidine-related piperidines as the basic component in antidiarrheal compounds results in retention of activity. The fact that the base is not directly related to a narcotic presumably leads to greater selectivity of action on the gut. Ring scission of butyrolactone 98 (obtainable by alkylation of a diphenylacetate ester with ethylene oxide) with hydrogen bromide gives the bromo acid 99. This is then converted to the dimethylamide by successive treatment with thionyl chloride and dimethylamine. The initial product from this reaction (100) is not observed as it undergoes spontaneous internal displacement to the cyclic imino ether salt 101. Treatment of 101 with amine 102 proceeds at the activated ether carbon to give fluperamide (103);²³ the same reaction with amine 103 affords the antidiarrheal agent loperamide (105).²³

Incorporation of additional basic centers into the phenylpiperidinol nucleus leads to a molecule that shows local anesthetic rather than CNS activity. Condensation of the protected piperidone 106 with



phenylmagnesium bromide affords the desired piperidinol (107). Alkylation of the carbinol by means of 2-chlorotriethylamine gives the corresponding basic ether (108). Hydrolysis of the carbamate protecting group (109), followed by alkylation of the resulting secondary amine with N-(chloroethyl)aniline affords the local anesthetic, diamocaine (110).²⁴



The piperidines discussed thus far contained a single polar substituent on the heterocyclic ring. Except for the last entry, the compounds all showed activity on the CNS or closely related systems. It is thus somewhat surprising to find that simple addition of an aroyl group leads to a compound that shows antiinflammatory activity. The seemingly complex molecule can in fact be obtained in two steps from simple starting materials.²⁵ Thus, Mannich reaction of p-fluoroacetophenone with paraformaldehyde and methylamine affords condensation product *111*. Treatment with aqueous base leads to cyclization by

internal aldol condensation. There is thus obtained the nonsteroidal antiinflammatory agent flazalone (112).²⁶



REFERENCES

- J. Hughes, T. W. Smith, H. W. Kosterlitz, L. A. Fothergill, B. A. Morgan and H. R. Morris, *Nature*, 258, 577 (1975).
- J. Fishman, U. S. Patent 3,152,042 (1964); Chem. Abstr., 61: 16111f (1964).
- N. Sharghi and L. Lalezari, Nature, 213, 1244 (1967).
- 4. U. Weiss, J. Am. Chem. Soc., 77, 5891 (1955).
- 5. For more detailed discussion, see D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, 290 (1975).
- Anon., French Patent, M6358 (1968); Chem. Abstr., 74: 141,577h (1971).

- 7. H. Blumberg, I. J. Pachter and Z. Matossian, U.
 S. Patent 3,332,950 (1967); Chem. Abstr.,
 67: 100301 (1967).
- K. W. Bently and D. G. Hardy, Proc. Chem. Soc., 220 (1963).
- K. W. Bentley, British Patent 1,136,214 (1968); Chem. Abstr., 70: 78218b (1969).
- D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, 292 (1975).
- I. Monkovic, H. Wong, B. Belleau, I. J. Pachter and Y. G. Perron, Can. J. Chem., 53, 2515 (1975).
- I. Monkovic and T. T. Conway, U. S. Patent
 3,775,414 (1973); Chem. Abstr., 80: 37349 (1974).
- I. Monkovic, H. Wong, A. W. Pircio, Y. G. Perron,
 I. J. Pachter and B. Belleau, Can. J. Chem., 53, 3094 (1975).
- 14. N. F. Albertson, U. S. Patent 3,382,249 (1968); Chem. Abstr., 69: 96509w (1968).
- 15. R. Grewe and A. Mondon, Chem. Ber., 81, 279 (1948).
- 16. W. F. Michne and N. F. Albertson, J. Med. Chem., 15, 1278 (1972).
- D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, 302 (1975).
- 18. W. Soudyn and I. Van Wijngaarden, German Patent 1,953,342 (1970); Chem. Abstr., 73, 38571g (1970).
- 19. E. M. S. Kreider, German Patent 2,161,865 (1972); Chem. Abstr., 17: 139818f (1972).
- 20. P. A. J. Janssen, German Patent, 1,807,691 (1969); Chem. Abstr., 71: 81194g (1969).

- 21. P. A. J. Janssen, Belgian Patent 606,849 (1961); Chem. Abstr., 56: 12861i (1962).
- 22. Anon., French Patent 2,161,007 (1973); Chem. Abstr., 79: 146,415s (1973).
- 23. R. A. Stokbroekx, J. Vandenbenk, A. H. M. T. Van Heertum, G. M. L. W. Van Laar, M. J. M. C. Van der Aa, W. F. M. Van Beren and P. A. J. Janssen, J. Med. Chem., 16, 782 (1973).
- 24. B. Hermans, H. Verhoeven and P. A. J. Janssen, J. Med. Chem., 13, 835 (1970).
- 25. J. T. Plati and W. Wenner, U. S. Patent 2,489,669 (1949); Chem. Abstr., 44, 2555f (1950).
- 26. L. Levy and D. A. McLure, U. S. Patent 3,408,445 (1968); Chem. Abstr., 70: 47302 (1969).

11

Five-Membered Heterocycles Fused to One Benzene Ring

1. INDOLES

The classic and most convenient synthesis of the indole moiety is that of Emil Fischer. Recent examples of its use for drug synthesis includes one preparation of the nonsteroidal antiinflammatory agent, *indoxole* (2).¹ Reaction of ketone *1* with phenylhydrazine in acetic acid leads directly to *indoxole* (2). Alternately, anisoin (3) can be reacted



with aniline by heating in concentrated HCl, proceeding presumably through direct displacement of OH by aniline followed by cyclodehydration to 2. A credible but more involved mechanism can also be written starting with Schiff's base formation.

A somewhat more complex example of the Fischer indole synthesis is provided by the tranquilizer, milipertine (8).² It can be prepared by reaction of



l-chlorobutan-3-one (4) with l-(2-methoxyphenyl)
piperazine (5), which leads to asymmetrical ketone 6.
Reaction of 6 with 3,4-dimethoxyphenylhydrazine leads
to complex hydrazone 7 which, on treatment with
strong acid, rearranges to milipertine (8). The
course of the last reaction reveals one of the classic

features of the Fischer synthesis-cyclization onto the more substituted side of the ketone. Another tranquilizer, *alpertine* (9), has a rather similar structure to 8.



Interest in the psychotropic features of the mushroom substance, *psilocybine*, led to an exploration of the chemistry of 4-hydroxyindole (10). The availability of this substance provided a suitable starting point for the synthesis of *pindolol* (12), a β -adrenergic blocking agent.³ Reaction of 10 with epichlorohydrin and NaOH led to ether 11 whose halo atom was readily displaced by isopropylamine to complete the synthesis of 12.

One of the more convenient methods of adding a twocarbon side chain to the electron-rich 3-position of indoles is the Speeter-Anthony reaction,⁴ illustrated in the synthesis of the antiadrenergic agent, solypertine (15).⁵ In this case, the reaction between 5,6-methylenedioxyindole and oxalyl chloride gives ketoacid chloride 13. The sequence then proceeds by amide formation (14) with amine 5. Reduction with



lithium aluminum hydride reduces both carbonyls to give solypertine (15) whose structural relationship to milipertine (8) is obvious. Another related drug is oxypertine (16), an antidepressant made by essentially the same route as illustrated for solypertine.⁵

Combining the nucleophilicity of the indole 3position just illustrated and the well-known tendency of C-2 and C-4 vinyl pyridines to add nucleophiles, a convenient synthesis of the tranquilizer *benzindopyrine* (19) was devised.⁶ Reaction of <u>N</u>-benzylindole (17) with 4-vinylpyridine (18) in acetic acid produced 19 directly.

Tryptamine and serotonin are naturally occurring indole ethylamino compounds with pronounced pharmacological activities. They have served as the inspiration for synthesis of numerous analogues. One such study involved alkylation of 4-benzamidopyridine (21)



with 2-(3-indolyl)ethylbromide (20) to give quaternary salt 22; this intermediate was in turn hydrogenated with a Raney nickel catalyst to give *indoramin* (23), which is antihypertensive, apparently because of its α -adrenergic blocking activity.⁷


Because of the resonance stabilization possible in its deprotonated form, the 5-tetrazolyl moiety is actually nearly as acidic (pKa <u>ca</u>. 6) as many carboxylic acids. This has led to its inclusion in many drug series as a carboxyl surrogate. Apparently related in concept to indomethacin (26a), intrazole (26) is a nonsteroidal antiinflammatory agent which also inhibits platelet aggregation, and therefore is of potential value in keeping the contents of the



vascular bed free-flowing in certain pathological conditions. The synthesis begins with 2-(3-indoly1)acetonitrile (24) which is transformed to the tetrazoy1 derivative (25) by 1,3-dipolar reaction with sodium azide. The acidic indole NH hydrogen is abstracted when 25 is treated with two equivalents of sodium hydride and the salt, when acylated with a single equivalent of 4-chlorobenzoyl chloride, is smoothly transformed to *intrazole*.⁸ Note that acylation occurs preferentially at the more nucleophilic (indole) anion.

When the indole 3-position is already substituted, electrophilic reagents attack the 2-position instead often through a 3,3-spiro intermediate. For example, when 2-(3-indoly1)ethylmercaptan (27) reacts with methyl acetoacetate, the thia- β -carboline analogue 31 results. It seems plausible that the reaction involves initial hemithioketal formation (28), followed by electron release by the indole nitrogen and hydroxide



displacement to give 29. Compound 29 has interrupted aromaticity, and a Wagner-Meerwein type rearrangement would led to carbonium ion 30, which would eject a proton to restore indole resonance (31). In any case, 31 is the product. Saponification to the free acid (32 is followed by dimethylamide formation (33), mediated by carboxyl activation via mixed anhydride reaction with ethyl chlorocarbonate. Lithium aluminum hydride reduction to the tertiary amine (34) is followed by base-mediated N-alkylation with ethyl bromide to produce tandamine (35), an antidepressant that inhibits the uptake of norepinephrine into storage granules.⁹

Yohimbine (36) is a well-known and reasonably available alkaloid from Corynanthe yohimbe, inter alia. For this reason, and partly because of its intrinsic pharmacological activity (including reputed aphrodisiac activity), chemists have frequently studied its properties. Oppenauer oxidation is usually attended by saponification and decarboxylation in this series, and yohimbone (37) is the product. Wolf-Kischner reduction to yohimbane (38), followed by sodium hydride mediated alkylation, leads to the analgesic agent, mimbane (39).



2. REDUCED INDOLES

Although geneologically related to indoles, the dihydroindoles behave chemically rather like alkyl anilines. When diphenylamine reacts with chloropropionyl chloride, amide 40 results; this in turn readily cyclizes to oxindole 41. Sodium hydride followed by 2-chloroethyldimethylamine alkylates the 3-position (possibly through an intermediate aziridinium ion); partial demethylation is accomplished by refluxing with ethylchlorocarbonate, followed by hydrolysis of the intermediate carbamate to give indolinone 42, the antidepressant amedalin.¹¹ Repetition of this sequence on the chloropropyl homologue, followed by reduction of the appropriate indolinone produces dihydroindole 43, daledalin, which also has antidepressant activity.¹¹





348

Hydrazides also containing a metasulfonamide function are known to exhibit diuretic activity. Substitution of an N-aminodihydroindole for the hydrazine is consistent with this activity. Preparation of one such agent is carried out by reaction of 2-methyl-N-aminoindoline (44) with 3-sulfamoyl-4chlorobenzoyl chloride (45), leading to the diuretic indapamide (46).¹²



A more highly oxidized indole relative is isatin (47). The ketonic carbonyl group is nonenolizable and has interesting properties. In strong acid it



becomes protonated, and the oxygen can be replaced by electron-rich moieties. Almost 100 years ago such a condensation with phenol was discovered to lead to 48. Acetylation led to oxyphenisatin (49) which has carthartic properties.¹³

It is also clearly anticipated that the ketonic moiety will form normal carbonyl derivatives. When isatin (47) is treated with sodium hydride and methyl iodide, the acidic hydrogen is alkylated to produce 50. Then, reaction of the ketone carbonyl with thiosemicarbazine leads to methisazone (51).¹⁴ At the time of its discovery, methisazone was one of a very few antiviral leads showing activity in whole animal tests, and led to an extensive exploration of the properties of analogues.



3. INDAZOLES

The compounds of medicinal interest in this group so far have all been nonsteroidal antiinflammatory agents or analgesics. The prototype is *benzydamine* (55).¹⁵ An interesting alternate synthesis of this substance starts by sequential reaction of N-benzylaniline with phosgene, and then with sodium azide to produce carbonyl azide 52. On heating, nitrogen is evolved and a separable mixture of nitrene insertion product 53 and the desired ketoindazole 54 results. The latter reaction appears to be a Curtiustype rearrangement to produce an N-isocyanate (54a), which then cyclizes. Alkylation of the enol of 54



54a)

with sodium methoxide and 3-dimethylaminopropyl chloride gives *benzydamine*.¹⁶ Alternatively, use of chloroacetamide in the alkylation step followed by acid hydrolysis produces bendazac (56) instead.¹⁷ Bendazac, an acetic acid derivative, more closely resembles the classical nonsteroidal antiinflammatory agents.

Reduction of the benzene ring is also compatible with activity in this group. Reaction of N-methyl-2-thiocarbamoylcyclohexanone (57) with methyl hydrazine produces the analgesic agent, tetrydamine (59), probably with the intermediacy of alkylhydrazone 58.¹⁸



4. BENZIMIDAZOLES

The control of worm infestations of domestic animals (horse, sheep, cattle, pigs) and humans is an important therapeutic objective for which *thiabendazole* (60) serves as the prototype of numerous benzimidazole derivatives.¹⁹ A widely used synthesis of this system is illustrated by the preparation of oxibendazole (62).²⁰ First, 4-hydroxyacetamide is alkylated by use of KOH and <u>n</u>-propyl bromide, and the product is nitrated to give 61. The latter compound is



hydrolyzed, reduced to the phenylenediamine with SnCl₂, converted to the 2-aminobenzimidazole system

by S-methylthiourea and subsequently acylated by methylchloroformate to produce 62. Lobendazole



(63),²¹ albendazole (64),²² oxfendazole (65),²³ mebendazole (66),²⁴ and cyclobendazole (67)²⁴ are all made by fairly obvious variants on this basic scheme. Cambendazole (69), best of 300 antihelmintic agents in an extensive study, is made by nitration of thiabendazole (60) to 68, followed by catalytic reduction and acylation with isopropyl chloroformate.²⁵





Flubendazole (70) belongs in this chemical class and is synthesized by similar methods but its bioactivity is expressed as an antiprotozoal agent.

At least in one case, a seemingly minor variation in the overall structure, change to the benzimidazolinone system, considerably alters the nature of



the bioactivity exhibited. Treatment of 4-chloro-Nphenylbenzimidazolinone (71) with t-BuOK and 3bromopropylchloride leads to halide 72, which itself undergoes halogen displacement on heating with dimethylamine to produce the antidepressant, *clodazon* (73).²⁶

5. MISCELLANEOUS

The pharmacological properties of *khellin* (74) have inspired a continuing interest in analogues. Change of the pyrone ring to a benzofuran ring results in a uricosoric agent, *benzbromarone* (78). In its preparation, Friedel-Crafts acylation of 2-ethylbenzofuran (75) with 4-methoxybenzoyl chloride leads to ketone 76, which undergoes ether cleavage to phenol 77 on

354

heating with pyridine hydrochloride; subsequent bromination produces *benzbromarone* (78).²⁷



Another khellin-inspired benzofuran is the cardiotonic and vasodilating agent, benfurodil (84).28 The reported synthesis begins by Reformatsky reaction between zinc, 4-methoxyacetophenone and ethyl bromo-The alcoholic function is dehyacetate to give 79. drated with tosic acid, NBS leads to the allylic bromide (80a) via the Wohl-Ziegler procedure, and then SN₂ displacement with NaOAc produces acetoxyketone Treatment with HCl then closes the butenolide 80b. ring to give 81. A Fries rearrangement, followed by demethylation, acetylation, and then ether formation with bromoacetone gives 82, which condenses to form the furan ring on base treatment; then sodium borohydride reduction produces alcohol 83. The synthesis

of *benfurodil (84)* is concluded by reaction with succinic anhydride and pyridine.



Probably inspired by *ibuprofen* and its analogues, the nonsteroidal antiinflammatory agent *benoxaprofen*



Fused Five-Membered Heterocycles

(91) is synthesized by starting with substituted aniline $85.^{29}$ A Sandmeyer-type sequence of diazotization (86) and acid hydrolysis leads to phenol 87, which undergoes nitration (88) and reduction to give aminophenol 89. Hydrolysis of the nitrile and esterification produces ester 90, which is converted to *benoxaprofen* (91) by acylation with 4-chlorobenzoyl chloride, followed by cyclization and then by saponification of the ethyl ester.

A catecholamine potentiator that apparently operates by inhibition of norepinephrine reuptake and that also inhibits gastric secretion is *talopram* (94). Its specific synthesis is hard to locate, but a general approach to this class of substance is available in the literature.³⁰ A suitable sequence would start from gem-dimethylphthalide 92 by reaction with phenyl Grignard reagent, followed by perchloric



acid dehydration of the tertiary carbinol to give oxonium ion 93. Reaction of 93 with 3-dimethylaminopropyl magnesium chloride would lead to the tertiary

357

amino analogue of 94. Demethylation would be accomplished by refluxing with ethyl chlorocarbonate, and the synthesis of *talopram* could be concluded by hydrolysis of the intermediate carbamate.

REFERENCES

- J. Szmuszkovicz, E. M. Glenn, R. V. Heinzleman, J. B. Hester, Jr., and G. A. Youngdale, J. Med. Chem., 9, 527 (1966).
- S. C. Laskowski, French Patent 1,551,082 (1968); Chem. Abstr., 72: 43,733v (1970).
- Anon., Netherlands Application 6,601,040 (1966); Chem. Abstr., 66: 18,669x (1967).
- M. E. Speeter and W. C. Anthony, J. Am. Chem. Soc., 76, 6209 (1954).
- S. Archer, D. W. Wylie, L. S. Harris, T. R. Lewis, J. S. Schulenberg, M. R. Bell, R. K. Kulling and A. Arnold, J. Am. Chem. Soc., 84, 1306 (1962).
- A. P. Gray and W. L. Archer, J. Am. Chem. Soc., 79, 3554 (1957).
- J. L. Archibald and J. L. Jackson, South African Application 6803204 (1969); Chem. Abstr., 72: 121,363r (1970).
- P. F. Juby and T. W. Huidyma, J. Med. Chem., 12, 396 (1969).
- 9. D. A. Demerson, German Patent 2,301,525 (1975); Chem. Abstr., 85: 103,883z (1976); W. Lippmann and T. A. Pugsley, Biochem. Pharmacol., 25, 1179 (1976).

358

- 10. J. Shavel, Jr., and M. Von Strandtmann, French Patent 1,405,326 (1965); Chem. Abstr., 63: 13,342a (1965).
- 11. A. Canas-Rodriguez and P. R. Leeming, J. Med. Chem., 15, 762 (1972).
- 12. L. Beregi, P. Hugon and M. Laubie, French Patent 2,003,311 (1969); Chem. Abstr., 72: 100,500t (1970).
- 13. A. Baeyer and M. J. Lazarus, Ber., 18, 2641 (1885).
- 14. D. J. Bauer and P. W. Sadler, Brit. J. Pharmacol., 15, 101 (1960).
- D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 323 (1977).
- 16. G. Palazzo, G. Corsi, L. Baiocchi and B. Silvesterini, J. Med. Chem., 9, 38 (1966); L. Baiocchi, G. Corsi and G. Palazzo, Ann. Chim. (Roma), 55, 116 (1965).
- 17. G. Palazzo, U. S. Patent 3,470,194 (1969); Chem. Abstr., 72: 110,697n (1970).
- G. Massaroli, L. Del Corona and G. Signorelli, Boll. Chim. Farm., 108, 706 (1969).
- 19. D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 326 (1977).
- 20. Anon., British Patent 1,123,317 (1968); Chem. Abstr., 69: 722k (1968).
- 21. P. P. Actor and J. F. Pagano, Belgian Patent 66,795 (1966); Chem. Abstr., 65: 5307g (1966).
- 22. R. J. Gyurik and V. J. Theodorides, U. S. Patent 3,915,986 (1975); Chem. Abstr., 84: 31,074r

(1976).

- 23. E. P. Averkin, C. C. Beard, C. C. Dvorak, J. A. Edwards, J. H. Fried, J. G. Killian, R. A. Schlitz, T. P. Kistner, J. H. Druoge, E. T. Lyons, M. L. Sharp and R. M. Corwin, J. Med. Chem., 18, 1164 (1975).
- 24. J. L. H. Van Gelder, A. H. M. Raeymaekers and L.
 F. C. Roevens, German Patent 2,029,637 (1971);
 Chem. Abstr., 74: 100,047s (1971).
- 25. D. R. Hoff, M. H. Fisher, R. J. Bochis, A. Lusi, F. Waksmunski, J. R. Egerton, J. J. Yakstis, A. C. Cuckler and W. C. Campbell, *Experientia*, 26, 550 (1970).
- 26. Anon., Belgian Patent 659,364 (1965); Chem. Abstr., 64: 2,093d (1966).
- 27. N. P. BuuHoi, E. Basagni, R. Royer and C. Routier, J. Chem. Soc., 625 (1957).
- 28. J. Schmidt, M. Susquet, G. Callet, J. Le Meur and P. Comoy, Bull. Soc. Chim. France, 74 (1967); J. Schmidt, M. Susquet, P. Comoy, J. Bottard, G. Callot, T. Clim and J. Le Meur, *ibid.*, 953 (1966).
- 29. D. W. Dunwell, D. Evans, T. A. Hicks, C. H. Cashin and A. Kitchen, J. Med. Chem., 18, 53 (1975).
- 30. F. J. McEvoy, R. F. Church, E. N. Greenblatt and G. R. Allen, Jr., J. Med. Chem., 15, 1111 (1972).

¹² Six-Membered Heterocycles Fused to One Benzene Ring

The prevalence of heterocyclic rings among drugs and biochemical agents of mammalian origin can lead to the erroneous assumption that the presence of such rings in drugs means that this moiety of necessity constitutes part of the pharmacophore. As was noted in the case of the monocyclic heterocycles, these ring systems, in fact, often merely serve the function of a generalized aromatic system. The SAR of such molecules frequently demonstrates that the heterocyclic ring can be replaced by some other moiety with comparable electron distribution and lipophilicity without loss of biological activity. Sometimes, however, a given heterocyclic system does constitute part of the pharmacophore. Replacement of the particular ring system in such cases leads to loss of the desired biological activity. Recognition of pharmacophoric functions is today still largely an empirical

art, although susceptible to experimental inquiry. It is expected that art will more closely approach science with the emergence of a deeper understanding of the mechanisms of action of drugs on the molecular level, and the increasing frequency with which receptors are now being isolated and studied.

1. QUINOLINES

The quinoline antimalarial agents constitute one of the earliest examples of pharmacophoric heterocyclic systems. It was recognized in the 1930's that chloroquinolineamines bearing an additional amino group in the side chain were often endowed with activity against the plasmodia that cause malaria.¹ Further exploration of these molecules led to an agent with antiamebic activity. Mannich condensation of quinolol l with paraformaldehyde and N,N-diethylpropylenediamine affords the antiamebic agent, *clamoxyquin* (3).²



The structures of drugs that have proven clinically useful for treatment of hypertension tend to fall into discrete classes according to their mode of action. It is thus usually a safe assumption that a drug containing a guanidine function will show the properties of a peripheral sympathetic blocking agent; also, phenoxypropanolamines and some phenylethanolamines will be effective by virtue of their β -adrenergic blocking activity. Experimental agents on the other hand tend to show much greater structural diversity; by the same token, it is more difficult to relate mode of action to structure in these cases. It is thus of note that a rather simple aminoquinoline shows hypotensive activity.

The synthesis of this aminoquinoline starts with one of the standard sequences for preparation of 4hydroxyquinolines, i.e., with the formation of the Shiff base (5) from the appropriately substituted aniline and diethyl oxaloacetate. Thermal cyclization gives the quinolone (6); this then spontaneously tautomerizes to the enol form (7). Saponification followed by decarboxylation gives the desired guinolol Treatment of 8 with phosphorus oxychloride (8). leads to replacement of the hydroxyl group by chlorine (9).³ Displacement of halogen by ammonia leads to the corresponding amine, probably by an additionelimination mechanism. There is thus obtained amquinsin (10), ⁴ a hypotensive agent. Formation of the Shiff base of amquinsin with veratraldehyde gives *leniquinsin (11)*,⁵ possibly a prodrug.

A related and relatively simple quinoline derivative has been reported to exhibit antidepressant activity. Its preparation merely involves displacement of halogen in 12 with piperazine to afford quipazine (13).⁶



Fused Six-Membered Heterocycles

Derivatives of phenylethanolamine substituted by a phenolic hydroxyl on the para position have been known for some time to exhibit β -adrenergic agonist activity. As a consequence of this property, the compounds have proven useful as bronchodilators for the treatment of asthma (see Chapter 3). Since such sympathomimetic drugs tend to have undesired activity on the cardiovascular system in addition to the desired activity on the bronchii, considerable work has been devoted to the preparation of compounds that would show selectivity for the adrenergic receptors (β_2) that predominate in the lung. Attachment of the side chain to a heterocyclic aromatic phenol has been one avenue that has shown promise for achieving this selectivity.

Halogenation of the acetyl compound 14 affords the corresponding chloroketone (15). (Compound 14 is obtainable by acylation of the quinolol. The pyridine ring is, of course, deactivated in the acidic conditions of the reaction.) Displacement of halogen by means of isopropylamine leads to the aminoketone



(16). Reduction of the carbonyl group by means of sodium borohydride goes in a straightforward manner to give the aminoalcohol, *quinterenol* (17).⁷ It is a reasonable assumption that the heterocyclic system in this case simply serves as a surrogate benzene ring.

Modern methods for raising poultry tend to concentrate large numbers of birds in a very small space. Although economically very attractive, the resulting dense population is an ideal setting for the extremely fast spread of avian epidemics, particularly those respiratory infections spread by droppings. The single-celled parasitic coccidia pose a particular threat to poultry flocks under these conditions. Considerable work has thus been devoted to the development of poultry coccidiostats. The rapidity with which these parasites develop resistance to chemotherapeutic agents serves as impetus for the development of a constant flow of drugs with new structures.

The "quinates" constitute the prototype for the quinoline poultry coccidiostats; many such agents can be prepared using the following general synthetic schemes. For example, alkylation of catechol with isopropyl bromide affords ether 18. Nitration perforce affords derivative 19. Catalytic reduction of the nitro group followed by condensation of the resulting aniline (20) with dimethyl ethoxymethylene malonate (21) affords the anil 22. The reaction is most reasonably rationalized by assuming a conjugate addition-elimination sequence. Heating of the last intermediate in Dowtherm affords the coccidiostat



proquinolate (23).⁸ The same sequence using cyclopropylmethyl bromide as alkylating agent for catechol and, later, diethylmethoxymethylenemalonate affords cyproquinate (28).⁹

The synthesis may be varied by reversing the alkylation and nitration steps. Thus for example, intermediate 25 can be obtained by alkylation of nitrocatechol 29. The difference in reactivity of the two phenolic groups in 29 (meta and para to an electron withdrawing group, respectively) may be used to prepare derivatives carrying different alkyl groups on each of the catechol oxygens. Alkylation of 29 with decyl bromide gives ether 30; reaction of the remaining phenolic function with ethyl iodide then gives 31. This intermediate then is converted to decoquinate $(34)^{10}$ when subjected to the rest of the synthetic sequence.





(<u>37</u>)

Replacement of one of the ethereal oxygen atoms by a methylene group is compatible with anticoccidial activity. For example, condensation of substituted aniline 35 with dimethyl ethoxymethylenemalonate affords aminoacrylate 36. Thermal cyclization in diphenyl ether gives *nequinate* (37).¹¹

Replacement of the remaining ether oxygen by basic nitrogen leads to a compound that shows antimalarial activity. Nitration of aniline derivative 38 leads to substitution para to the alkyl group. (Protonation of the amine under the reaction conditions leads to deactivation of the position para to that group relative to that para to alkyl. The position meta to the protonated amine is less deactivated.)



Reduction of the newly introduced nitro moiety affords aniline 40. This is then subjected to the familiar condensation-cyclization sequence to give antimalarial amouinate (42).¹²

Alkylation on nitrogen in this class leads to compounds with antibacterial activity, apparently due to inhibition of DNA gyrase. Condensation of aniline derivative 43 with diethyl ethoxymethylenemalonate, followed by cyclization of the resulting intermediate affords the guinoline 44. Alkylation with ethyl iodide by means of sodium hydride in DMF gives the corresponding N-ethyl compound. (Deprotonation of 44 leads to an ambident anion: alkylation at nitrogen may be favored by the greater nucleophilicity and steric accessibility of that atom.) Saponification of the ester affords oxolinic acid (46).¹³ This compound interestingly again illustrates the interchangeability of aromatic rings; the prototype antibacterial agent, *nalidixic acid* (47), ¹⁴ contains a



1,8-naphthyridine ring system and can be considered an azaquinolone.

Reduction of either ring of quinolines greatly alters biological activity. Although the agent in which the carbocyclic ring is reduced can be considered a substituted pyridine, it is included here because it is prepared by using chemistry more akin to that of quinolines. Condensation of the cyclohexanedione derivative 48 with the malondialdehyde enol ether 49 leads directly to the tetrahydroquinoline 51. The sequence can be envisaged as involving first an addition-elimination reaction to afford, after double bond migration, intermediate 50; aldol cyclization will then afford the observed product.





Reduction of the carbonyl group by Wolff-Kishner reaction gives intermediate 52.¹⁵ Treatment of that compound with butyl lithium gives the corresponding

metalated derivative (53); reaction of 53 with trimethylsilyl isothiocyanate affords the corresponding thioamide. There is thus obtained the gastric antisecretory agent *tiquinamide* (54).¹⁶ This synthetic sequence is of special interest in that direct chemical reduction of quinolines usually results in reduction of the heterocyclic ring.

Reduction of the heterocyclic ring and incorporation of a nitro function affords a compound with antischistosomal activity, oxamniquine (60). Its synthesis begins with chlorination of 2,6-dimethylquinoline, which proceeds regiospecifically on the methyl group adjacent to the ring nitrogen (56).



Fused Six-Membered Heterocycles

Displacement of halogen by isopropylamine gives intermediate 57. High pressure catalytic hydrogenation leads to reduction of the heterocyclic ring (58), and nitration proceeds <u>para</u> to the NH group (59). Microbiological oxidation of the methyl group in that last intermediate using Aspergillus sclerotorium affords oxamniquine (60).¹⁷

2. ISOQUINOLINES

As has been noted elsewhere, blockers of α -adrenergic receptors often bear little structural resemblance to the phenylethanolamines which are the endogenous agonists. A relatively simple tetrahydroisoquinoline derivative in fact shows hypotensive activity by virtue of its α -adrenergic blocking properties. Alkylation of tetrahydroisoquinoline itself with bromochloropropane gives intermediate 62. Displacement of the halogen with sodium ethylmercaptide gives thioether 63. Oxidation of sulfur by means of peracetic acid is stopped at the sulfoxide stage to afford esproquin (64).¹⁸



The use of β -adrenergic agonists as bronchodilators is discussed in some detail in Chapter 3. As mentioned there, requirements for activity include the phenylethanolamine side chain and a phenolic hydroxyl group or its equivalent disposed para to the It is of note that the side chain hydroxyl side chain. can be omitted from molecules that contain the full catechol substitution of epinephrine with retention of good activity. One such compound, trimethoquinol (71), which in addition contains the side chain sterically constrained by cyclization to a tetrahydroisoquinoline has proven to be a clinically useful bronchodilator. Condensation of trimethoxybenzaldehyde with ethyl chloroacetate under Darzens conditions gives the glycidic ester 66; this is then converted to the sodium salt (67). This salt is then treated with dopamine (69) under conditions which will cause decarboxylation and rearrangement of 67 to the corresponding aldehyde (68). The reaction conditions are coincidentally the same as those of the Pictet-Spengler synthesis. Thus, the intermediate aldehyde reacts with the amine to form carbinolamine 70 or the corresponding imine. This then cyclizes to the tetrahydroisoquinoline, trimethoquinol (71).¹⁹ Interestingly, only the 1-S isomer is an active bronchodilator.

Guanidines attached to a group of appropriate lipophilicity have proven to be useful antihypertensive agents, active by virtue of their peripheral sympathetic blocking activity. *Debrisoquine* (72) is in fact used clinically for that indication.²⁰ The 7-bromo analogue (76) also shows antihypertensive



activity, and can be prepared as follows. Diazotization of the aminodihydroisoquinoline 73, followed by conversion of the diazonium salt to the bromide by heating in the presence of HBr, affords intermediate 74. Reduction of the imine function with sodium borohydride gives the saturated heterocycle 75. Condensation of this secondary amine with S-methylthiourea affords guanisoquin (76).²¹



(76)

Formation of blood clots is a process necessary for maintenance of the integrity of the circulatory system. Any break in the system results in clotting to seal off the potential leakage. The final step in the process involves stabilization of the clot by a protein called fibrin. A number of pathological conditions result in the formation of clots within the circulatory system in the absence of injury. Such clots--also known as emboli--present a serious hazard by their potential for blocking circulation of blood to vital organs. The considerable research devoted to agents that will lyse the fibrin in clots has led to the development of the clinically useful agent, *urokinas*e. This drug is a fibrinolytic proteinaceous enzyme isolated from human urine. The difficulty involved in isolation of significant amounts and the antigenicity of urokinase and a related

microbial product, streptokinase, has led to the search for simple molecules that will accomplish the A tetrahydroisoguinoline derivative (80) same end. has shown this activity in animal test systems. Its formation involves classical isoguinoline chemistry, and begins with acylation of two molar equivalents of phenethylamine 77 with adipic acid to afford the diamide 78. Ring closure of the amide by means of phosphorus oxychloride gives the usual Bischler-Napieralski product 79--although with an intervening butylene chain. Reduction of the imine by means of sodium borohydride affords the fibrinolytic agent, bisobrin (80).²²







Products of Bischler-Napieralski cyclizations discussed thus far have been reduced in order to afford the desired biologically active compounds. Occasionally, the products obtained directly from the cyclization have biological activity in their own right. In one example, acylation of 2-phenethylamine with p-chlorophenoxyacetyl chloride affords the amide 83; then, cyclization by means of phosphorus pentoxide gives the antiviral agent famotine (84).²³ The same sequence starting with the p-methoxy acid chloride 85 gives memotine (87), an antiviral agent.²³



The majority of nonsteroidal antiinflammatory agents contain an acidic carboxyl group. A series of experimental agents in this class have been prepared in which the acidic proton is supplied by a highly enolizable proton from a function such as a β -dicarbonyl incorporated into a heterocyclic system. As an example, an acylated, highly oxidized isoquinoline moiety can fulfill this function (see also the benzothiazines below). Toward this end, reaction of homophthalic acid with ammonia affords the imide 89; triethylamine catalyzed condensation of that intermediate with p-chlorophenylisocyanate affords the corresponding amide. There is thus obtained the antiinflammatory agent tesicam (90). 24



3. QUINAZOLINES

Quinazolines containing an electron-rich carbocyclic ring have been associated with smooth muscle relaxant activity. The mechanism of action (phosphodiesterase inhibition, α - adrenergic blockade) and organ selectivity (bronchi, vascular smooth muscle) vary greatly with substitution on the heterocyclic ring.

Nitration of 3,4-dimethoxypropiophenone (91)affords the nitro derivative 92, and catalytic reduction leads to the aminoketone (93). This is then converted to the corresponding formamide by means of formic-acetic anhydride. Treatment with ammonia completes construction of the quinazoline ring. There is thus obtained the bronchodilator-cardiotonic agent, quazodine (95).²⁵

In a similar vein, condensation of the substituted anthranilamide 96 with trimethyl orthoformate affords directly the quinazolone 98. Reaction with phosphorus



oxychloride converts the carbonyl to the enol chloride (99). Displacement of halogen with monosubstituted


piperazine 100 gives the bronchodilator *piquizil* (102);²⁶ the same reaction with piperazine 101 leads to another bronchodilator *hoquizil* (103).²⁷

A similar scheme is used to construct a quinazoline containing halogen at both positions 2 and 4. The differences in reactivity of these halides make available compounds bearing two different amine substituents. Nitration of aldehyde 104, followed by oxidation affords the acid 106. The acid is then converted to the primary amide (107), and the nitro group is reduced catalytically to the corresponding





amine (108). Condensation with urea completes construction of the heterocyclic ring (109); this is converted to the desired dichloride by reaction with phosphorus oxychloride (110). Reaction with ammonia in THF at room temperature serves to replace the more reactive chlorine by a primary amine (111). Displacement of the remaining halogen is achieved with piperazine under more strenuous conditions (112). Alkylation of the piperazine nitrogen with allyl bromide affords the antihypertensive agent quinazocin (113).²⁷ Acylation at the same position gives the recently commercialized antihypertensive agent prazosin (114).²⁸

The same scheme starting with 3,4,5-trimethoxybenzaldehyde (115) affords initially dichloroquinazoline 116. Reaction of this intermediate with ammonia leads to replacement of the amine at the 2-position (117). Displacement of the remaining chlorine with piperazine carbamate 101 affords the antihypertensive agent trimazocin (118).²⁹



The extensive series of antibacterial agents consisting of derivatives of 5-nitrofurfural has been discussed in Chapter 8. It is of interest that a

382

derivative of nitrofuran in which the carbonyl is at the acid oxidation stage and incorporated into a quinazoline also shows antibacterial activity; this agent, *nifurguinazol (124)*, is prepared as follows. Treatment of the amide from 5-nitrofuroic acid with phosphorus oxychloride leads to the corresponding This intermediate is then converted nitrile (120). to the iminoether (121) with ethanolic hydrogen chloride.³⁰ Condensation with anthranilic acid in the presence of sodium methoxide gives the quinazolone The amide function is then converted to the 122. iminochloride with phosphorus oxychloride (123). Replacement of halogen by means of diethanolamine affords nifurquinazol (124).³¹



Benzothiadiazines containing halogen and a sulfonamido group on the carbocyclic ring (125) form a large class of diuretic agents often referred to as the thiazides; the ring sulfone group can be replaced by carbonyl with retention of significant biological activity.³² More recently, it has been found that diuretic activity is retained when one of the ring nitrogen atoms carries an aryl group. Toward this end, the starting aniline 127 is first acetylated (128) by means of acetic anhydride to protect the primary amine in subsequent steps. Reaction with chlorosulfonic acid leads to sulfonyl chloride 129; this is converted to the sulfonamide by reaction with ammonia (130). Oxidation of the methyl group by means of permanganate cleanly gives the acid 131; the acetyl group is then removed by hydrolysis. Treatment of the resulting anthranilic acid (132) with phosgene then leads to the isatoic anhydride 133. Reaction of that anhydride with ortho-toluidine results in acylation of that aniline by the anthranilic acid (134); tying up the anthranilic acid up as the anhydride serves to both activate the carbonyl towards amide formation and to protect the amine towards self condensation. The carbamic acid presumably formed as an intermediate decarboxylates. Treatment of the anthranilamide 134 with acetic anhydride affords directly guinazolone 135. (The sequence may be rationalized by assuming acetylation of the aniline as the first step; formation of an imine between the carbonyl and amide nitrogen gives the observed product.) Reduction of the imine function with sodium borohydride in the presence of aluminum chloride gives the diuretic agent metolazone (136).³³



The majority of nonsteroidal antiinflammatory agents contain some function which supplies an acidic proton, be this a carboxyl group or a highly activated enol system. A quinazolone devoid of such potential enolizable protons forms an interesting exception to this generalization. (It is tempting in such cases to speculate that the compound may exert its biological activity by some mechanism distinct from the rest of the class.) Alkylation of aminobenzophenone 137 with isopropyl iodide gives the corresponding N-alkylated amine (138). Treatment of that intermediate with urethane in the presence of zinc chloride serves to form the quinazolone ring. The reaction may be rationalized by assuming acylation of the amine as the first step to form urea 139. Intramolecular imine formation then affords the observed antiinflammatory product, proquazone (140).³⁴



A more highly oxidized derivative of quinazoline forms the heterocyclic moiety of a compound with CNS activity. Condensation of the aminopropylpiperazine 141 with isatoic anhydride gives the anthranilamide 142. Reaction of that amide with phosgene gives directly the heterocyclic ring. (The reaction may proceed by initial formation of the carbamoyl chloride;



(143)

this may then either acylate the amide or alternatively decompose to an isocyanate. This last could then add the amide nitrogen.) The product of this sequence is the sedative: tranquilizer *cloperidone* (143).³⁵

4. CINNOLINES AND QUINOXALINES

Replacement of a methine in oxolinic acid (46) by nitrogen is apparently consistent with retention of antibacterial activity. One approach begins with reduction of nitroacetophenone 144 to afford the corresponding aminoketone (145). Treatment of this intermediate with nitrous acid leads to the diazonium salt; the diazonium group condenses with the ketone methylene group (as its enol form) to lead to the cyclized product, cinnoline 147. Bromination proceeds at the position adjacent the enol grouping (148);



then displacement by means of cuprous cyanide (149) followed by alkylation on nitrogen affords cyanoketone 150. Hydrolysis of the nitrile function then gives cinoxacin (151), ³⁶ an antibacterial agent.

The pyrazole derivative phenylbutazone (152) has found extensive clinical use as an antiinflammatory agent. (The acidic proton here is generated by a β-dicarbonyl system.) Incorporation of salient portions of the molecule in a condensed heterocycle yields a compound, cintazone (160), which also exhibits antiinflammatory activity. The synthesis of 160 starts with Grignard addition of methylmagnesium bromide to ortho-aminobenzophenone (153), affording carbinol 154; dehydration gives the corresponding olefin (155). The cinnoline ring is then constructed by a sequence similar to that used above. Thus treatment of the amine with nitrous acid gives the diazonium salt; treatment with mild base (ammonium hydroxide) causes the salt to close to the cinnoline (157). Catalytic reduction in acetic acid affords initially the product (158) of 1,4-addition of hydrogen; this product is in tautomeric equilibrium with cyclic hydrazine 159. Condensation of 159 with diethyl amylmalonate leads to formation of the pyrazolodione There is thus obtained cintazone (160). 37 ring.

Oxidation of 2,3-dimethylquinoxaline (from phenylenediamine and diacetyl) with either peracids or hydrogen peroxide in acetic acid gives the 1,4dioxide (*162*). ³⁸ Treatment of this bis-N-oxide with selenium dioxide leads to oxidation of one of the methyl groups to the methyl carbinol and formation of

388















(<u>160</u>)

CH3

`Сн₃

N + 0

(<u>162</u>)















mediquox (163), 39 an agent used to treat respiratory infections of poultry. Reaction of 162 with selenium dioxide under more strenuous conditions proceeds to the aldehyde stage (164). Condensation of the carbonyl group with methyl carbazate affords carbadox (165). 40 The biological activity of carbadox is similar to that of mediquox.

5. MISCELLANEOUS BENZOHETEROCYCLES

Partial reduction of lactone *166* (using for example diisobutylaluminum hydride in the cold) affords lactol *167*. Condensation with nitromethane leads to the corresponding alkylated tetrahydrobenzopyran *170*. The sequence probably starts by aldol reaction of the hydroxylactone form of the lactol (*168*) with nitromethane to give the vinyl nitro intermediate *169*;



intramolecular conjugate addition of the alcohol will then give the observed product. Since this last step is in principle reversible, the reaction is expected to yield predominantly the thermodynamically favored bisequatorial cis isomer. Catalytic reduction of the nitro group then gives the primary amine anorectic agent fenisorex (171).⁴¹

Condensation of 2,4-dihydroxypropiophenone (172) with benzoyl chloride and sodium benzoate goes to afford chromone 174, probably via ester 173. This procedure is known as the Kostanecki-Robinson reaction. Methylation (175) of the remaining phenolic function by means of dimethyl sulfate, followed by reaction



with formaldehyde and hydrogen chloride gives the chloromethyl intermediate 176. Displacement of chlorine with dimethylamine then affords the respiratory stimulant dimefline (177). 42

Modification of the substitution pattern on the same chromone gives a compound with smooth muscle relaxant activity, flavoxate (184). The synthesis of this flavone ester is initiated with methylation of the hydroxypropiophenone 177 to 178 followed by reduction of the nitro group to yield aniline 179. The amine is then used to introduce a nitrile by diazotization followed by treatment of the diazonium salt with cuprous cyanide (180); the methyl ether is then cleaved by means of aluminum chloride. Treatment of the phenolic ketone 181 with benzoyl chloride and sodium benzoate serves to build up the chromone ring The nitrile is next hydrolyzed to the acid (182).with sulfuric acid. Esterification of the carboxyl as--its acid chloride--with N-(2-hydroxyethyl)piperidine affords *flavoxate* (184). 43



Reaction of salicylamide *185* (obtainable from a suitable activated derivative of salicylic acid and N,N-diethylethylenediamine) with ethyl chloroformate

in the cold followed by heating affords the benzoxazinedione 187.⁴⁴ It is likely that the transformation proceeds via carbonate 186; the product, letimide (187), is reported to show analgesic activity.



Among the heterocyclic systems that have been used to provide a backbone for acidic, nonsteroidal antiinflammatory agents are benzo-1,2-thiazine dioxides, such as 193-195. Entry to the ring system is gained by an interesting ringenlarging rearrangement. The necessary intermediate for the expansion reaction is prepared by alkylation of saccharin (188) with ethyl bromoacetate to afford the ester 189. Treatment of that with sodium methoxide results in formation of the anion adjacent to the carbonyl; bond reorganization gives the net result (190) of a ring enlargement. The driving force for the reaction may well reside in the fact that the anion of the product is a weaker base than that of starting material. Sodium hydroxide mediated alkylation of the product (190) with methyl iodide might occur at any one of three sites (O, N or C) due to the multidentate nature of the anion; interestingly, the reaction proceeds to give only the N-methylated product (192). 45 Amide formation from

192 by interchange with 2-aminothiazole affords the antiinflammatory agent sudoxicam (193);⁴⁶ the same reaction using 2-aminopyridine gives pyroxicam (194).⁴⁶ Formation of the amide from 192 and 3-amino5-methylisoxazole leads to isoxicam (195).⁴⁷



As noted above, a convenient pathway to cinnolines consists of intramolecular condensation of a diazonium group with a ketonic methyl group, or alternately with a double bond. The analogous reaction with an amide nitrogen leads to 1,2,3-benzotriazines, such as 198. Reaction of isatoic anhydride with Naminomorpholine affords the hydrazide 196; then, treatment with nitrous acid yields initially the diazonium salt (197). Under the reaction conditions this cyclizes to the triazine 198, the analgesic agent molinazone.⁴⁸ This must be one of the few--if not the only--compound containing a linear array of four nitrogens ever to be tried in the clinic.



Changing the substitution pattern on the carbocyclic ring of the benzothiadiazine diuretics is well known to have a marked effect on the qualitative biological activity. Thus, the direct analogue of the diuretic *chlorothiazide* (199) in which chlorine replaces one sulfonamide group, *diazoxide* (200), shows negligible diuretic activity; instead the compound is a potent antihypertensive vasodilator. The same pattern of activity is maintained in a closely related analogue. Condensation of aminosulfonamide 201 with aldehyde 202 affords the saturated heterocyclic system (203); oxidation with silver nitrate leads to the antihypertensive agent *pazoxide* (204).





- For a fuller discussion, see D. Lednicer and L.
 A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 341 (1975).
- J. H. Burckhalter, W. S. Brinigar and P. E. Thompson, J. Org. Chem., 26, 4070 (1961).
- A. R. Surrey and H. F. Hammer, J. Am. Chem. Soc., 68, 113 (1946).
- F. F. Ebetino and G. C. Wright, French Patent 1,388,756 (1965); Chem. Abstr., 63: 589c (1965).
- 5. A. Winterstein, U. S. Patent 3,272,806 (1966); Chem. Abstr., 65: 18567 (1966).
- R. Rodriguez, German Patent 2,006,638 (1970); Chem. Abstr., 73: 98987g (1970).

- Anon., Netherlands Patent, 6,601,980 (1966); Chem. Abstr., 66: 115616k (1967).
- E. J. Watson, Jr., Belgian Patent 640,906 (1964); Chem. Abstr., 63: 2962 (1965).
- R. H. Mizzoni, F. Goble, J. Szanto, D. C. Maplesden, J. E. Brown, J. Boxer and G. De Stevens, *Experientia*, 24, 1188 (1968).
- J. J. Ball, M. Davis, J. N. Hodgson, J. M. S. Lucas, E. W. Parnell, B. W. Sharp and D. Warburton, Chem. Ind., 56 (1970).
- 11. Anon., Netherland Application 6,602,994 (1966); Chem. Abstr., 68: 68899j (1968).
- 12. R. L. Clark, A. A. Patchett, E. F. Rogers, U. S. Patent 3,377,352 (1968); Chem. Abstr., 71: 38821x (1969).
- 13. D. Kaminsky and R. I. Meltzer, J. Med. Chem., 11, 160 (1968).
- D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, 492 (1975).
- 15. A. C. W. Curran, J. Chem. Soc., Perkin Trans. I, 975 (1976).
- 16. A. C. W. Curran and R. G. Shepherd, J. Chem. Soc., Perkin Trans. I, 983 (1976).
- 17. H. C. Richards, South African Patent 6803,636 (1968); Chem. Abstr., 71: 30369k (1969).
- 18. A. P. Gray and R. H. Shiley, J. Med. Chem., 16, 859 (1973).
- E. Yamato, M. Hirakura and S. Sugasawa, Tetrahedron Suppl., 8, 129 (1966).
- 20. D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, 351 (1975).

- 21. R. C. Koch, Belgian Patent 635,308 (1964); Chem. Abstr., 61: 11978g (1964).
- J. L. Fliedner, Jr., J. M. Schor, M. J. Myers and I. J. Pachter, J. Med. Chem., 14, 580 (1971).
- 23. Anon., Netherlands Application 6,516,328 (1966); Chem. Abstr., 65: 15351b (1966).
- 24. S. B. Kadin, South African Patent 68 03,465 (1968); Chem. Abstr., 70: 115025z (1969).
- 25. J. L. Minielli and H. C. Scarborough, French Patent M3207 (1965); Chem. Abstr., 63: 13287 (1965).
- 26. T. H. Cronin and H.J. E. Hess, South African Patent 67 06512 (1968); Chem. Abstr., 70: 68419 (1969).
- 27. Anon., British Patent 1,156,973 (1969); Chem. Abstr., 71: 91519f (1969).
- 28. T. H. Althuis and H.J. Hess, J. Med. Chem., 20, 146 (1977).
- 29. H.J. Hess, German Offen., 2,120,495 (1971); Chem. Abstr., 76: 127012e (1972).
- 30. W. R. Sherman and A. von Esh, J. Med. Chem., 8, 25 (1965).
- 31. H. A. Burch, J. Med. Chem., 9, 408 (1966).
- 32. D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, 354-360 (1975).
- 33. B. V. Shetty, L. A. Campanella, T. L. Thomas, M. Fedorchuk, T. A. Davidson, L. Michelson, H. Volz, S. E. Zimmerman, E. J. Belair and A. P. Truant, J. Med. Chem., 13, 886 (1970).
- 34. H. Ott and M. Denzer, German Patent 1,805,501 (1969); Chem. Abstr., 71: 30502 (1969).

- 35. S. Hayao, H. J. Havera, W. G. Strycker, T. J. Leipzig, R. A. Kulp and H. E. Hartzler, J. Med. Chem., 8, 807 (1965).
- 36. W. A. White, German Patent 2,065,719 (1975); Chem. Abstr., 83: 58860k (1975).
- 37. F. Schatz and T. Wagner-Jauregg, Helv. Chim. Acta, 51, 1919 (1968).
- 38. J. K. Landquist and G. J. Stacey, J. Chem. Soc., 2822 (1953).
- 39. J. D. Johnston, U. S. Patent 3,344,022 (1967); Chem. Abstr., 67: 111452b (1967).
- 40. J. D. Johnston, Belgian Patent 669,353 (1965); Chem. Abstr., 65: 7196e (1966).
- 41. M. W. Klohs, F. J. Petracek, J. W. Bolger and N. Sugisaka, South African Patent 72 00,748 (1973); Chem. Abstr., 79: 126310a (1973).
- P. da Re, L. Verlicchi and I. Setnikar, Arzneimittelforsch., 10, 800 (1960).
- 43. P. Da Re, L. Verlicchi and I. Setnikar, J. Med. Chem., 2, 263 (1960).
- 44. H. J. Havera and S. Hayao, South African Patent 67 07,712 (1968); Chem. Abstr., 70: 87821k (1969).
- 45. J. G. Lombardino, E. H. Wiseman and W. M. McLamore, J. Med. Chem., 14, 1171 (1971).
- 46. J. G. Lombardino and E. H. Wiseman, J. Med. Chem., 15, 849 (1972).
- 47. H. Zinnes, M. Schwartz and J. Shavel, Jr., German Patent 2,208,351 (1972); Chem. Abstr., 77: 164722c (1972).

Fused Six-Membered Heterocycles

- 48. H. Herlinger, S. Petersen, E. Tietze, F. Hoffmeister and W. Wirth, German Patent 1,121,055 (1962); Chem. Abstr., 56: 15523e (1962).
- 49. J. G. Topliss and A. J. Wohl, Swiss Patent 558,376 (1975); Chem. Abstr., 82: 156390f (1975).

¹³ Benzodiazepines

That the benzodiazepines continue to be prominent on the list of the 200 most frequently prescribed drugs in the United States is both a commentary on the nature of our contemporary society and a measure of their acceptance as anxiolytic and tranquilizing substances. Intensively competitive research into new analogues continues and this chapter chronicles some of the more prominent members of this group not detailed in the original volume.

The original entries into this class, such as chlordiazepoxide (1), were N-oxides.¹ Treatment of the N-acetate (2) of chlordiazepoxide with aqueous acid served to hydrolyze the acylenamine function to liberate the keto analogue (3) which has been identified in excreta as an active metabolite of 1; this minor tranquilizer has been named demoxepam.²



It will perhaps be recalled from the earlier volume that such N-oxides are prone to undergo the Polonovski rearrangement when treated with acetic anhydride, and that this was illustrated by the formation of oxazepam.¹ It is not surprising that the N-methyl analogue (4) also undergoes this process, and hydrolysis of the resulting acetate gives temazepam (5).³ Care must be exercised with the conditions, or the inactive rearrangement product 6 results.



The lactam moiety in benzodiazepines is active toward nucleophiles and numerous analogues have been made by exploiting this fact. For example, heating *demoxepam (3)* with N-cyclopropylmethylamine leads to amidine formation, the minor tranguilizer *cyprazepam* (7).⁴ On the other hand, treatment of diazepam (8)



with phosphorus pentasulfide produces the corresponding thionamide, *sulazepam* (9), also a minor tranquilizer.⁵ The thionamide moiety is even more



(10)

 $(\underline{11})$

prone to aminolytic amidine formation than the lactam itself. Reaction of thionamide 10 with <u>0</u>-allyl-hydroxylamine gave the oximinoether 11, uldazepam.⁶

An attempt to reduce metabolic N-dealkylation resulted in the preparation of *fletazepam* (16), whose activity is expressed as a muscle relaxant.⁷ Direct N-alkylation of the amide NH group at a late stage in the synthesis with trifluoroethyl iodide and NaH went in poor yield, so the desired alkyl group was introduced at an earlier stage. Alkyation of 4-chloroaniline by the trichloromesyl ester of trifluoroethanol (12) produced secondary aniline 13. This underwent alkylation by aziridine to produce diamine 14. Acylation with 2-fluorobenzoyl chloride produced





the desired secondary amide which underwent Bischler-Napieralski cyclodehydration with $POCl_3$ and P_2O_5 to give 15. The lactam moiety was introduced by ruthenium tetroxide oxidation to give *fletazepam* (16). Interestingly, the deoxy analogue minus the fluorine atom, prepared by a similar route,⁷ is also a minor tranguilizer. A rather interesting synthesis of the basic ring system based upon oxidative scission of indole precursors was used to prepare prazepam (24), a muscle relaxant.⁸ Starting with indole 17, N-alkylation to 18 was accomplished with cyclopropylmethyl bromide and NaH. The ester was converted to the amide (21) by the usual sequence and then reduced to primary amine 22 using lithium aluminum hydride.



Oxidation with chromium trioxide in acetic acid cleaved the indole ring to produce intermediate 23 which cyclodehydrated to give prazepam (24).

Nitration of benzodiazepines takes place at the electron rich C₇ position, and this was used to prepare *flunitrazepam* (25), a potent hypnotic agent.⁹

It is interesting to note that some 1,5-benzodiazepines such as 29 also possess CNS depressant activity. Treatment of substituted diphenylamine 26 with methyl malonyl chloride and reduction with Raney nickel led to orthophenylenediamine analogue 27. Sodium alkoxide treatment led to lactam formation (28), and alkylation in the usual way with NaH and methyl iodide produced *clobazam* (29).¹⁰



On the other hand, MnO_2 oxidation of lactam 30 or arylation of secondary lactam 32 with bromobenzene using Cu powder and potassium acetate both led to anxiolytic triflubazam (31).¹¹

406



REFERENCES

- D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, p. 365, 1977.
- L. H. Sternbach and E. Reeder, J. Org. Chem., 26, 4936 (1961).
- S. C. Bell and S. J. Childress, J. Org. Chem., 27, 1691 (1962).
- 4. H. M. Wuest, U. S. Patent 3,138,586 (1964); Chem. Abstr., 61: 7,032f (1964).
- 5. G. A. Archer and L. H. Sternbach, J. Org. Chem., 29, 231 (1964).
- J. B. Hester, Jr., German Patent 2,005,176 (1970); Chem. Abstr., 73: 99,001t (1970).
- M. Steinman, J. G. Topliss, R. Alekel, Y.S. Wong and E. E. York, J. Med. Chem., 16, 1354 (1973).
- S. Inaba, T. Hirohashi and H. Yamamoto, Chem. Pharm. Bull., 17, 1263 (1969).
- L. H. Sternbach, R. I. Fryer, O. Keller, W. Metlesics, G. Sach and N. Steiger, J. Med.

Chem., 6, 261 (1963).

- K.H. Weber, A. Bauer and K.H. Hauptmann, Ann., 756, 128 (1972).
- 11. K.H. Weber, H. Merz and K. Ziele, German Patent 1,934,607 (1970); Chem. Abstr., 72: 100,771g (1970); and K.-H. Weber, K. Minck, A. Bauer and H. Merz, German Patent 2,006,601 (1971); Chem. Abstr., 76: 3918k (1972).

¹⁴ Heterocycles Fused to Two Benzene Rings

Pharmacological agents based on dibenzo heterocyclic compounds had their inception in the formal cyclization by inclusion of a hetero bridging atom of the two benzene rings characteristic of diphenylamine and benzhydryl antihistamines. As detailed in the earlier volume, this approach led to the development of the first of the antipsychotic agents, chlorpromazine. Further modification of the central ring led to compounds that showed antidepressant rather than tranquilizing activity. It might be noted in passing that it was eventually discovered that the central ring in antidepressants need not be heterocyclic at all; some of the more widely used antidepressant drugs are in fact derivatives of dibenzocycloheptadiene. Further modification of the dibenzoheterocycles has not yielded agents with markedly different activities. The compounds discussed below, with few exceptions,

exhibit either antihistaminic or central nervous system activity.

CENTRAL RING CONTAINING ONE HETEROATOM 1. Reaction of 2-bromobenzoic acid (1) with chlorosulfonic acid proceeds to afford the sulfonyl chloride 2; treatment with dimethylamine leads to the corresponding sulfonamide (3). Condensation of bromoacid 3 with the anion from thiophenol in the presence of copper powder results in displacement of halogen by sulfur (4). Friedel-Crafts cyclization of that sulfide by means of sulfuric acid gives the desired thioxanthone (5), which is then reduced to the thioxanthene (6). Treatment of that intermediate with butyl lithium serves to form the anion at the methylene group; the corresponding acyl derivative 7 is obtained by condensation of the anion with methyl acetate. Mannich reaction on the ketone with formaldehyde and N-methylpiperazine yields the amino ketone (8). The carbonyl group is then reduced with sodium borohydride. Dehydration by means of phosphorus oxychloride in pyridine gives the major tranquilizer thiothixene (10).¹ As might be expected, this last reaction gives a mixture of isomers; the more active Z isomer is separated from the mixture by fractional crystallization.

The presence of a rather more complex substituent on the remote piperazine nitrogen atom is consistent with tranquilizing activity. The preparation of one such agent, 16, begins with reaction of thioxanthone 11 (obtained by a sequence analogous to that used to



prepare 5) with the Grignard reagent from 3-(tertiaryamyloxy)propyl bromide to afford alcohol 12. Treatment with hydrogen bromide serves to dehydrate the carbinol, remove the protecting group from the terminal alcohol,

and finally to convert that alcohol to the corresponding bromide (13). Although this would be expected as a mixture of isomers, the sharp melting point of the product suggests it may be homogenous. This halide is then used to alkylate the monocarbamate from piperazine, yielding 14. Saponification of the carbamate affords the secondary amine 15. Michael condensation of that base with N-methylacrylamide gives the neuroleptic agent, *clothixamide* (16).²



Reduction of the exocylic double bond and inclusion of the side chain nitrogen in a piperidine ring leads to a compound (19) which exhibits skeletal muscle relaxant activity. Its one step synthesis begins with reaction of thioxanthene (17) with phenyl sodium to afford the anion at the methylene group of the heterocycle; then, condensation of that anion with piperidine derivative 18 gives directly methixene (19).³



Lucanthone (20) constitutes one of the first effective antischistosomal agents. Biological investigation of this agent showed that the active species in man is in fact the hydroxylated metabolic product hucanthone (21). The published synthesis for the latter involves microbial oxidation as the last step.⁴ Additional hydroxylated derivatives of lucanthone have been investigated. One of these, becanthone (26), made as part of an investigation of antitumor agents, shows activity against schistosomes comparable to that of hycanthone. Ullmann reaction of the salt of thiophenol 22 with 2-chlorobenzoic acid in the presence of copper gives the sulfide 23. Ring closure by means of sulfuric acid gives the corresponding thioxanthone (24). Nucleophilic aromatic substitution of the chlorine atom in 24 with aminoalcohol 25 gives becanthone (26) directly.⁵



The thioxanthene tranquilizers described above may be regarded as phenothiazine analogues in which a methine group acts as surrogate for nitrogen; that is, the side chain is attached to sp₂ carbon instead It is thus of some interest that further, of nitrogen. rather drastic, modification of the central ring still gives a compound with tranquilizing activity. In the case of clomacran (30), the side chain is again attached to carbon, albeit tetrahedral rather than trigonal carbon. In addition, the sulfur atom present in both phenothiazines and thioxanthenes is replaced by a secondary amine. This might be interpreted to mean that the nature of the bridge between the benzene rings is not crucial for biological activity. The preparation of 30 begins with reaction of acridone 27 with the Grignard reagent from 3-chloro-N,N-dimethylpropylamine to afford tertiary carbinol 28; dehydration by means of acid or simply heat gives the corresponding olefin (29). Catalytic reduction completes the synthesis of the tranquilizer, clomacran $(30).^{6}$



Nuclei for tricyclic antidepressants and tranquilizers almost invariably contain the three rings fused in linear array. It is thus interesting to note that an angular arrangement of these rings, such



as in *fantridone* (32), is consistent with antidepressant activity. Alkylation of the anion obtained by treatment of phenathridone (31) with sodium hydride and 3-chloro-N,N-dimethylpropylamine affords *fantridone* (32) directly.⁷

Almost every major structural class discussed to date has featured at least one nonsteroidal antiinflammatory carboxylic acid. It is thus perhaps not surprising to find a dibenzoheterocycle serving as the nucleus for one of these agents, furobufen (34). Straightforward Friedel-Crafts acylation of dibenzofuran (33) with succinic anhydride affords a mixture of 2- and 3-acylated products, with the latter predominating. The mixture is esterified with methanol, and the methyl ester of the 3-isomer is separated by fractional crystallization. Hydrolysis back to the acid affords pure 34.⁸



Replacement of sulfur in the phenothiazines by two methylene groups also results in compounds that retain antipsychotic activity; two examples are *carpipramine* (41) and *clocapramine* (44). Although one might describe this as yet another example of the bioisosteric equivalence of sulfur and ethylene, the observed broad latitude in the nature of the tricyclic system in tranquilizers suggests caution in drawing such a conclusion. In a convergent synthesis of 41, reaction of N-benzyl-4-piperidone (35) with potassium cyanide and piperidine hydrochloride gives the corresponding α -aminonitrile (36). Hydrolysis of the nitrile by means of 90% sulfuric acid gives the amide
Heterocycles Fused to Two Benzene Rings

37; hydrogenolysis of the benzyl protecting group then affords the secondary amine 38.⁹ Alkylation of dibenzazepine 39 with 1-bromo-3-chloropropane gives intermediate 40. Use of that material to alkylate piperidine 38 affords finally carpipramine (41).¹⁰ The same sequence starting with halogen substituted dibenzazepine 42 leads to the tranquilizer clocapramine (44).¹⁰



Many tricyclic tranquilizers and antidepressants exhibit some measure of anticholinergic activity. It is of interest to note that attachment of a basic side chain on carbon of an isomeric dibenzazepine affords a compound in which anticholinergic activity predominates, *elantrine* (50). Reaction of anthraquinone (45) with the Grignard reagent from 3-chloro-N,N-dimethylaminopropane in THF in the cold results in addition to but one of the carbonyl groups to yield hydroxyketone 46. This is then converted to oxime 47 in a straightforward manner. Treatment of that intermediate with a mixture of phosphoric and polyphosphoric acids results in net dehydration of



the tertiary carbinol and Beckmann rearrangement of the oxime to afford the enelactam 48; the stereochemistry of the product(s) ($\underline{\mathbf{E}}, \underline{\mathbf{Z}}$) is not specified. The lactam is then reduced to amine 49 with lithium aluminum hydride, and the resulting amine is methylated to obtain elantrine (50).¹¹

Replacement of the ring nitrogen in 50 by oxygen yields a molecule that can now again be characterized as a tranquilizer, although one that shows some degree of anticholinergic activity. Synthesis of this agent, *pinoxepin* (55), begins with the reaction of 1,3-dibromopropane with triphenylphosphine to give the bromoalkylphosphonium salt 51. Displacement of the remaining bromine by piperazine then leads to the



functional phosphonium salt 52. The latter is then converted to the corresponding ylide by means of

butyl lithium, and the resulting reactive intermediate is condensed with ketone 53. The product (54) in this case consists largely (4:1) of the \underline{Z} isomer. The stereoselectivity may involve complexation of the betaine intermediate with the heterocyclic oxygen. Condensation of the terminal secondary amine with ethylene oxide affords pinoxepin (55).¹²

2. BENZOHETEROCYCLOHEPTADIENES

Both this and the previous volume are of course organized on the basis of structural classes. Occasionally, a series of medicinal agents defies attempts at neat classification by such a scheme. The compounds that follow could only be called dibenzoheterocycles by performing the imaginary operation of moving the hetero atom from the flanking to the central ring of the molecule. The chemistry and biological activity of those molecules does seem to argue for their inclusion at this juncture.

The first of these compounds, pizotyline (65), shows activity much akin to related tricyclic depressants such as *imipramine* (56).¹³ One of several schemes for preparation of the key tricyclic intermediate 63 starts by reaction of 2-chloromethylthiophene 57 with triethyl phosphite. The net transformation (Arbuzov reaction) probably starts with formation of phosphonium salt 58; displacement of one of the ethyoxy groups by chloride at carbon then leads to loss of ethyl chloride and formation of the observed phosphonate 59. Reaction of the ylide

420



obtained from the last intermediate with hemi phthalaldehyde (60) gives the diarylethylene 61. Reduction of the double bond (62), followed by Friedel-Crafts cyclization by means of polyphosphoric acid affords the requisite ketone 63. This compound is then condensed with the Grignard reagent from 1-methyl-4chloropiperidine, and the resulting carbinol (64) is dehydrated. There is thus obtained the antidepressant agent *pizotyline* (65). ¹⁴

Replacement of the thienyl grouping in 65 by pyridyl affords azatadin (75), a compound in which antihistaminic rather than antidepressant activity predominates. (It is of interest that the equivalent interchange in the acyclic series affords a pair of compounds each of which is an antihistamine.) The synthesis of the tricyclic system in this case starts by acylation of the anion from phenylacetonitrile with ethyl nicotinate to give cyanoketone 66. Hvdrolysis of the nitrile followed by decarboxylation of the resulting keto-acid gives ketone 67; reduction then leads to the diarylethane 68. Functionality is then introduced into the pyridine ring by the elegant method introduced by Taylor.¹⁵ Thus, treatment of 68 with peracid gives N-oxide 69; reaction of that with phosphorus trichloride leads to the corresponding 2chloropyridine (70) with simultaneous loss of the oxide. Displacement of halogen with cyanide followed by hydrolysis of the resulting nitrile (71) gives the carboxylic acid (72). Cyclization by means of polyphosphoric acid yields the key tricyclic intermediate 73. The ketone is then condensed with the Grignard



reagent from N-methyl-4-chloropiperidine to afford the carbinol 74. Finally, dehydration of this last intermediate affords the antihistamine *azatadin*e (75).¹⁶

A similar sequence starting with the acylation product (76) from metachlorophenylacetonitrile gives the halogenated tricyclic ketone 83. Condensation of that intermediate with ethyl bromoacetate in the presence of zinc (Reformatsky reaction) gives the hydroxyester 84. This product is then in turn dehydrated under acid conditions (85), saponified to the corresponding acid (86), and converted to the dimethylamide (87) by way of the acid chloride. The amide function is then reduced to the amine (88) with lithium aluminum hydride; catalytic hydrogenation of the exocyclic double bond completes the synthesis of closiramine (89).¹⁶ This compound also exhibits antihistaminic activity.

3. DERIVATIVES OF DIBENZOLACTAMS

A recurring theme in the present chapter has been the association of CNS activity with dibenzoheterocycles that bear a basic chain pendant from the central ring. As we have seen, considerable latitude exists as to the constitution of the central ring. The earlier volume in this series described the preparation of the antidepressant *dibenzepin (90)*, in which the basic function is attached to a lactam nitrogen.¹⁷ It has been found subsequent to this that attachment of the basic center in the guise of a piperazine ring as an amidine derivative again affords a series of compounds with activity on the CNS.

Preparation of the simplest of these examples (95) starts with hydrogenolysis of <u>o</u>-aminobenzoylbenzoic acid (91) with zinc (activated by copper) in ammonia. Thermal cyclization of the resulting diphenylmethane (92) gives the desired lactam (93).¹⁸ Treatment of that intermediate with phosphorus oxychloride in the presence of N,N-dimethylaniline leads to iminochloride 94. Aminolysis with N-methylpiperazine affords the hypnotic agent perlapine (95).¹⁹

Replacement of the bridge methylene group in 95 by a secondary amine is consistent with CNS activity, although the compound in this case (99) is described as a sedative agent. The synthetic approach used in this case relies on cyclization of an intermediate in which the piperazine ring is already in place. Thus, reaction of the acid chloride from 96 (available by Ullmann reaction of anthranilic acid on 2,5-dichloronitrobenzene) with N-methylpiperazine gives the corresponding amide (97). The nitro group is then reduced to yield aniline 98. Intramolecular dehydration then affords the amidine, *clozapine* (99).²⁰

Replacement of the methylene group in 95 by oxygen results in yet another subtle qualitative change in CNS activity. The products of this replacement, such as 104 and 111, are characterized as anxiolytic agents. In the synthesis of 104 we find yet a different approach to the amidine function, beginning with reaction of 2-chloronitrobenzene with

















(<u>94</u>)

(<u>90</u>)



 $(\underline{97})$ R = 0 (98) R = H



(<u>99</u>)

the anion from p-chlorophenol to afford the product of aromatic nucleophilic displacement (100); then, reduction of the nitro group affords the corresponding aniline (101). Treatment of that amine with phosgene in the presence of excess triethylamine converts the aniline to the isocyanate (102). Condensation of that intermediate with N-methylpiperazine affords urea 103. Bishler-Napieralski type cyclization of the urea into the adjacent ring is accomplished with phosphorus oxychloride. There is thus obtained loxapine (104).²¹







(<u>104</u>)

Another approach to this ring system leaves the formation of the oxygen bridge to the end. This scheme starts by reaction of the dichlorobenzoic acid 105 with carbonyldiimidazole (106) to afford the reactive intermediate 107. Condensation with o-aminophenol gives the amide 108, which is then converted to the iminochloride with phosphorus pentachloride. Condensation of 109 with piperazine apparently stops cleanly at monomer 110. Intramolecular Ullmann condensation in the presence of copper powder leads to formation of the dibenzoxazepin ring, and thus amoxapine (111).²²





Heterocycles Fused to Two Benzene Rings

Finally, replacement of the methylene bridge by a sulfur bridge leads to compounds such as 117 and 123 which are major tranguilizers. Thus, Ullmann condensation of thiosalicylic acid 112 with orthochloronitrobenzene affords thioether 113; the nitro group is then reduced to the aniline (114). Cyclization as above leads to the lactam 115, which is then converted to the iminochloride derivative (116). Condensation with N-methylpiperazine affords clothiapine (117), ²¹ Exactly the same sequence with the methyl substituted thiosalicylic acid derivative 118 leads to metiapine (123).²¹



 $(118) X = CH_{Z}$

(114) X = C1; R = H (119) $X = CII_{\tau}; R = 0$ (120) X = CH₃; R = H



 $(121) X = CH_3$



(117) X = C1 $(123) X = CH_3$

(116) X = C1 $(122) X = CH_{z}$

4. OTHER DIBENZOHETEROCYCLES

Historically, research in industrial medicinal chemistry has occurred in waves. The discovery of some novel structure with unique biological activity has often occasioned intensive work in numerous laboratories on the preparation and evaluation of analogues. Each such wave recedes when it is realized that further modification of the molecule is reaching the point of diminishing returns. At this juncture, the structure is often represented in the clinic by several commercialized drugs; it is judged unlikely that further work will produce a patentably novel compound that could make significant inroads on the market for drugs already available.

Nowhere, perhaps, is this phenomenon better illustrated than in the phenothiazine class. The earlier volume devoted a full chapter to the discussion of this important structural class, which was represented by both major tranquilizers and antihistamines. The lone phenothiazine below, flutiazin (130), in fact fails to show the activities characteristic of its class. Instead, the ring system is used as the aromatic nucleus for a nonsteroidal antiinflammatory agent. Preparation of 130 starts with formylation of the rather complex aniline 123. Reaction with alcoholic sodium hydroxide results in net overall transformation to the phenothiazine by the Smiles rearrangement. The sequence begins with formation of the anion on the amide nitrogen; addition to the carbon bearing sulfur affords the corresponding transient spiro intermediate 126. Rearomatization

affords thiophenoxide 127; this then attacks the adjacent ring and the resulting negative charge on the ring carbon adjacent to nitrogen is then discharged by expulsion of the nitro group as the nitrite anion. The formyl group on what is essentially a diphenylamine is sufficiently labile so that it too comes off under the reaction conditions. There is thus obtained the phenothiazine carboxylic ester 129. Saponification of the ester completes the synthesis of the veterinary antiinflammatory agent flutiazin (130).²³



 $(\underline{129})$ R' = CH₃ $(\underline{130})$ R' = H

(128)

(127)

The association between abnormally high levels of serum lipids and atherosclerosis has been discussed earlier. One of the earliest and still most widely used drugs for normalizing lipid levels and thus presumably treating atherosclerosis is the phenoxyester clofibrate (131). The wealth of analogues in this series has demonstrated that lipid lowering activity is retained when a second chlorophenoxy group is substituted onto the beta carbon of the acid moiety. More recently it was found that the two aromatic rings can be linked to form an eight-membered hetero-In one example, treatment of potassium dicycle. chloroacetate with the dipotassium salt of bisphenol 132 affords the dibenzoxacin 133 directly, after acidification. Esterification with methanol gives the hypolipidemic agent treloxinate (134).²⁴



REFERENCES

 B. M. Bloom and J. F. Muren, Belgian Patent 647,066 (1964); Chem. Abstr., 63: 11,512a (1965). Heterocycles Fused to Two Benzene Rings

- J. M. Grisar, U. S. Patent 3,196,150 (1965); Chem. Abstr., 63: 18,116f (1965).
- J. Schmutz, U. S. Patent 2,905,590; Chem. Abstr., 54: 5,699n (1959).
- 4. D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 399, 1977.
- E. J. Blanz, Jr., and F. A. French, J. Med. Chem., 6, 185 (1963).
- C. L. Zirkle, U. S. Patent 3,131,190 (1964); Chem. Abstr., 61: 4,326a (1964).
- 7. J. W. James and R. E. Rodway, British Patent 1,135,947 (1968); Chem. Abstr., 70: 87,603r (1969).
- G. Schilling and T. A. Dobson, German Patent 2,314,869 (1974); Chem. Abstr., 81: 25,527n (1974).
- 9. P. A. J. Janssen, U. S. Patent 3,041,344 (1962); Chem. Abstr., 59: 6,417b (1963).
- M. Nakanishi, C. Tashiro, T. Munakata, K. Araki,
 T. Tsumagari and H. Imamura, J. Med. Chem., 13,
 644 (1970).
- 11. Anon., Belgian Patent 652,938 (1965); Chem. Abstr., 64: 19,575h (1966).
- 12. Anon., Netherland Appl. 6,411,861 (1965); Chem. Abstr., 63: 16,366a (1965).
- D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 401404, 1977.
- 14. J.M. Bastian, A. Ebnother, E. Jucker, E. Rissi and A. P. Stoll, Helv. Chim. Acta, 49, 214 (1966).
- 15. E. C. Taylor, Jr., and A. J. Crovetti, J. Org. Chem., 19, 1633 (1954).

- 16. F. J. Villani, U. S. Patent 3,366,635 (1968); Chem. Abstr.,69: 10,372m (1968).
- 17. D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. I, p. 405, 1977.
- D. D. Emrick and W. E. Truce, J. Org. Chem., 26, 1239 (1961).
- 19. F. Hunziker, F. Kunzle and J. Schmutz, Helv. Chim. Acta, 49, 1433 (1966).
- F. Hunziker, E. Fischer and J. Schmutz, Helv. Chim. Acta, 50, 1588 (1967).
- 21. J. Schmutz, F. Kunzle, F. Hunziker and R. Gauch, Helv. Chim. Acta, 50, 245 (1967).
- 22. C. F. Howell, R. A. Hardy and N. Q. Quinones, French Patent 1,508,536 (1968); Chem. Abstr., 70: 57,923c (1969).
- B. M. Sutton, U. S. Patent 3,471,482 (1969);
 Chem. Abstr., 72: 21,701f (1970).
- J. M. Grisar, R. A. Parker, T. Kariya, T. Blohm,
 R. W. Fleming, V. Petrow, D. L. Wenstrup and
 R. G. Johnson, J. Med. Chem., 15, 1273 (1972).

¹⁵ β -Lactam Antibiotics

Despite the enormous effort already expended during the past three decades, the β -lactam antibiotic field remains one of the most hotly competitive in the whole field of medicinal chemistry, with new entities constantly being produced to address one or more the clinical deficiencies perceived in existing drugs. Recently, some new basic skeletons have been encountered in fermentation screening programs, and this has given the field yet another burst of activity. *Cefoxitin (31)* is the first fruit of this effort. Whether the nocardicins, clavulanic acid, thienamycins, etc., will reach the marketplace is not yet clear. Meanwhile, intensive work is still being done among the older ring systems.







Clavulanic Acids







R = H, $R = COCH_3$



Thienamycins



Nocardicins

1. PENICILLINS

The new entries in this section are the result of manipulation of polar amide side chains to broaden the antimicrobial spectrum of the penicillins. Carbenicillin (1) is used in the clinic primarily because of its low toxicity and its utility in treating urinary tract infections due to susceptible Pseudomonas species. Its low potency, low oral activity, and susceptibility to bacterial β -lactamases make it vulnerable to replacement by agents without these deficits. One contender in this race is *ticarcillin* Its origin depended on the well-known fact (to (4). medicinal chemists) that a divalent sulfur is often roughly equivalent to a vinyl group. One synthesis began by making the monobenzyl ester (2) of (3thienyl)malonic acid, converting this to the acid chloride with SOCl₂, and condensing it with 6-aminopenicillanic (6APA) acid to give 3. Hydrogenolysis (Pd/C) completed the synthesis of ticarcillin (4). 1



Ampicillin (5) remains the penicillin of choice for many infections because of its oral activity and good potency against Gram-negative bacteria. A number of prodrugs have been examined in attempts to improve upon its pharmacodynamic characteristics, and one of these is talampicillin (8).² One synthesis involved protecting the primary amino group of ampicillin (5) as the enamine with ethyl acetoacetate (6). This was then esterified by reaction with 3bromophthalide (7), and the enamine was carefully hydrolyzed with dilute HCl in acetonitrile to produce talampicillin (8).



In an attempt to form orally active penicillins unrelated to ampicillin, use was made of the fact that certain spiro α -aminoacids, such as 9, are well absorbed orally and transported like normal amino acids. Reaction of cyclohexanone with ammonium carbonate and KCN under the conditions of the Bucherer-Bergs reaction led to hydantoin 10. On acid hydrolysis, α -amino acid 11 resulted. Treatment with phosgene both protected the amino group and activated the carboxyl group toward amide formation (as 12) and reaction with 6-aminopenicillanic acid gave cyclacillin (13).³ Interestingly, this artifice



seems to have worked, since *cyclacillin* is more active <u>in vivo</u> than its <u>in vitro</u> spectrum suggests would be likely.

2. CEPHALOSPORINS

The oral activity and clinical acceptance of *cephalexin* (14) has led to the appearance of a spate of similar molecules. *Cefadroxyl* (16) is an example.⁴ The design of this drug would seem to have derived from the success of *amoxycillin*. The synthesis of *cefadroxyl* was accomplished by N-acylation of 7-aminodesacetyl-cephalosporanic acid (7 ADCA) after blocking the carboxy group with $(CH_3O)_2CH_3SiCl$ (to 15). The

blocking group was removed by solvolysis with butanol to give *cefadroxy1* (16).



Noting that 1,4-cyclohexadiene rings are nearly as planar as benzene rings but of greatly different reactivity, a cephalosporin was synthesized with such a moiety. Birch reduction of D- α -phenylglycine (17) led to diene 18. This was N-protected using tbutoxycarbonyl azide and activated for amide formation via the mixed anhydride method using isobutylchloroformate to give 19. Mixed anhydride 19 reacted readily with 2-aminodesacetoxycephalosporanic acid to give, after deblocking, cephradine (20).⁵



A more traditional cephalosporin analogue is cephapirin (22). It was made by reacting 7-aminocephalosporanic acid with bromoacetyl chloride to give amide 21. The halo group was displaced by 4-thiopyridine to give 22, cephapirin.⁶

One of the few successful analogues in the β lactam series with an aliphatic side chain is *ceph-acetrile (23)*. It was made by reacting 7-aminocephalosporanic acid with cyanoacetyl chloride in the presence of tributylamine.⁷



Modifications of the substituent at C_3 are conveniently accomplished using sulfur nucleophiles to displace the acetoxy moiety which is present in the fermentation products. *Cefamandole* (26) is such an agent. Reaction of 7-aminocephalosporanic acid with thiotetrazole 24 gave displacement product 25,



which was subsequently reacted with dichloroacetyl mandelate to put on the side chain. Deblocking during workup produced *cefamandole (26)*.⁸

Reaction of sodio 7-aminocephalosporanic acid with 1-(1H)-tetrazoylacetic acid gave intermediate 27. Reaction of this last with 2-mercapto-5-methyl-1,3,4-thiadiazole led to the widely used parenteral cephalosporin, cefazolin (28).⁹



3. CEPHAMYCINS

While screening for β -lactam antibiotics stable to β -lactamases, a strain of *Streptomyces lactamdurans* was found to contain several such agents which have a $6-\alpha$ -methoxy group whose electronic and steric properties protect the antibiotic from enzymatic attack. *Cephamycin C (29a)*, one of these substances, is not of commercial value, but side chain exchange has led to much more potent materials. Of the various ways of effecting this transformation, one of the more direct is to react cephamycin C with nitrous acid so that the aliphatic diazo product (*29b*) decomposes by secondary amide participation giving cyclic iminoether *30*. The imino ether moiety solvolyzes more readily than the β -lactam to produce 7-aminocephamycinic

442

acid, which was acylated in the usual way to produce cefoxitin (31) with broad spectrum activity and excellent resistance to bacterial degradation.¹⁰





REFERENCES

- Anon., Belgian Patent 646,991 (1964); Chem. Abstr., 63: 13,269f (1965).
- I. Isaka, K. Nakano, T. Kashiwagi, A. Koda, H. Horiguchi, H. Matsui, K. Takahashi and M. Murakami, Chem. and Pharm. Bull., 24, 102 (1976); J. P. Clayton, M. Cole, S. W. Elson, H. Ferres, J. C. Hanson, L. W. Mizen and R. Sutherland, J. Med. Chem., 19, 1385 (1976).
- 3. H. E. Alburn, D. E. Clark, H. Fletcher and N. H. Grant, Antimicrob. Agts. Chemother., 586 (1967).
- 4. T. Ishimaru and Y. Kodama, German Patent

2,163,514 (1973); Chem. Abstr., 79: 78,826z (1973).

- J. E. Dolfini, H. E. Applegate, G. Bach, H. Basch, J. Bernstein, J. Schwartz and F. L. Wiesenborn, J. Med. Chem., 14, 117 (1971).
- L. B. Crast, Jr., R. G. Graham and L. C. Cheney, J. Med. Chem., 16, 1413 (1973).
- Anon., Netherlands Patent 6,600,586 (1966); Chem. Abstr., 65: 20,131h (1966).
- 8. J. R. Guarini, U. S. Patent, 3,903,278 (1976).
- K. Kariyone, H. Harada, M. Kurita and T. Takano, J. Antibiotics, 23, 131 (1970).
- 10. L. D. Cama, W. J. Leanza, T. R. Beattie and B. G. Christensen, J. Am. Chem. Soc., 94, 1408 (1972); S. Karady, S. H. Pines, L. M. Weinstock, F. E. Roberts, G. S. Brenner, A. M. Hoinowski, T. Y. Cheng and M. Sletzinger, *ibid.*, 94, 1410 (1972).

¹⁶ Miscellaneous Fused Heterocycles

As may be apparent now, compounds in a given structural class are often associated with good biological activity. This means that on the operational level, a good many examples of those structures will be available that have been assigned generic names. Tn terms of this book, those compounds will merit a chapter or even a section. Thus, for example, although β -lactams represent a relatively narrow structural descriptor, activity in this class is sufficiently promising so that a full chapter is needed to fully cover those compounds. There does, however, exist a sizeable group of compounds that are not so readily categorized, since relatively few examples of each type have been assigned generic names. The medicinal agents discussed below are miscellaneous in that there is no readily apparent unifying thread in terms

of either structure or biological activity by which to group them, other than in a miscellaneous way.

Compounds with Two Fused Rings 1. Discovery in medicinal chemistry is intimately dependent on available animal test systems. Except for certain infectious diseases, it is rare to find a preexisting animal model for the human disease for which drugs are being sought. For example, animals do not develop atherosclerosis spontaneously. As a result, pharmacologists exercise great ingenuity in devising animal test systems intended to be relevant to diseases. Such assays, particularly in the area of agents acting on the CNS, are often quite indirect in that the connection to the human disease may be somewhat circuitous. Those tests are usually validated as far as possible with test results from drugs known to be active in the human. There thus exists the distinct possibility that an animal test will preordain the discovery of compounds that act by a closely similar mechanism, and thus have the same side effects, as those already on the market. This is perhaps best illustrated in the field of the centrally The animal tests in this area acting analgesics. have proven very reliable in detecting compounds that show analgesic activity in man; at the same time, all drugs discovered by these assays have at least some of the side effects of the prototype, morphine, to a greater or lesser degree. For this reason, therapeutic breakthroughs are relatively rare and celebrated events.

The discovery of an analgesic that acts by a presumably nonopiate pathway, in fact, resulted from a clinical trial of the compound in question, nefopam (4), in man. It might be noted that this trial was designed to study the drug as a muscle relaxant. It should also be noted that nefopam fails to show activity in many of the tests used to detect compounds with central analgesic activity. At the present time, there does not seem to exist any solution to that conundrum, short of the clearly unacceptable alternative of using man as the test animal. The huge expense and the bureaucratic requirements needed before embarking on a clinical trial in the late 1970's serve to make this kind of discovery less common and inclines the field more and more to modest advances in modulating potency or side effects. Does the old saw, "drugs are discovered in the clinic," still have relevance? Time will tell.

Preparation of *nefopam* starts with the acylation of aminobenzhydrol l (obtainable by reduction of the corresponding benzoylbenzamide) with chloroacetyl chloride; treatment of the chloroamide (2) with potassium tertiary butoxide results in internal alkylation to give the eight-membered ring (3). Reduction of the lactam function with lithium aluminum hydride gives the amine and, thus, *nefopam* (4).¹

Although most nonsteroidal antiinflammatory agents depend on the presence of an acidic proton for activity, examples of nonacidic drugs are scattered among the various structural classes. A furanopyrrole,



octazamide (11), represents yet another structure that has been found to act as a peripheral analgesic/ antiinflammatory agent. Hydrolysis of substituted furan 5 gives the corresponding diol (6), which is then reduced catalytically to afford the tetrahydrofuran 7. Both the method of reduction and the subsequent cyclization suggest that the product has the *cis* configuration. Reaction of 7 with tosyl chloride leads to ditosylate 8; use of that intermediate to bisalkylate benzylamine affords the bicyclic heterocyclic system (9). Debenzylation (10) followed by acylation of the resulting secondary amine with benzoyl chloride affords finally octazamide (11).²



One of the first pharmacological classes to be studied by medicinal chemists was local anesthetics. Many of the guiding principles which are used to this day, for example, molecular dissection, side chain substitution and inversion, and the like, were first developed in the course of those early researches. The most tangible fruit of that work was the development of a host of local anesthetic drugs; since there is a limited demand for such agents, the field lay quiescent for a good many years. The adventitious discovery that the local anesthetic agent lidocaine (12) showed antiarrhythmic activity in man has lent impetus to renewed interest in local anesthetics for new application. In particular, compounds are being sought which escape the main shortcoming of *lidocaine*; that drug is active for clinical purposes by intravenous administration only.

Preparation of one of these newer local anesthetic/antiarrhythmic agents, rodocaine (19), starts with the synthesis of an octahydropyrindene. Conjugate addition of the enolate from cyclopentanone to acrylonitrile gives the cyanoketone 13. The carbonyl group is then protected as its ethylene ketal (14), and the nitrile is reduced to the corresponding primary amine (15). Deketalization in dilute acid affords a transient aminoketone, which spontaneously cyclizes to the imine 16. Dissolving metal reduction (sodium in ethanol) affords the <u>trans</u>-fused bicyclo 17.³ (Catalytic reduction of 16 affords the cis isomer.



It is unexpected that the presumably thermodynamically controlled metal in alcohol reduction gives the trans compounds; the *cis* isomer is usually the more stable in the analogous all-carbon hydrindane system.) The amide portion of the molecule (18) is assembled by acylation of 2,6-dimethylaniline with 3-chloropropionyl chloride. Alkylation of 17 with chloroamide 18 affords rodocaine (19).⁴

2. Compounds with Three or More Fused Rings Preparation of rigid analogues of medicinal agents sometimes leads to compounds with greatly increased activity. Briefly, the success of a rigid analogue depends on locking a previously freely rotating side chain or flexible molecule into a conformation that will give a better fit with some putative receptor. Application of this principle to the tricyclic antidepressants does indeed afford a compound, mianserin (26), which retains the activity of the parent molecule. Preparation of 26 begins with acylation of the benzylaniline 20 (available from the benzophenone) with chloroacetyl chloride to give amide 21. Treatment with a mixture of phosphorus oxychloride and polyphosphoric acid leads to cyclodehydration of the amide to the corresponding tricyclic intermediate 22. Displacement of the now allylic chloride by means of methylamine gives the amine 23; this is then reduced to the diamine 24 with sodium borohydride. Construction of the last ring is accomplished by formation of the cyclic diamide (25) from 24 by ester interchange with diethyl oxalate. Reduction of this α -diamide with diborane proceeds with no apparent difficulty to

the diamine, the antidepressant compound mianserin (26).⁵



Application of the same type of reasoning to an anxiolytic benzodiazepine results in a rigid analogue, clazolam (35), which also retains the activity of the parent molecule, diazepam. It should be noted that in this case it is a benzene ring rather than a side chain that is conformationally restricted. Condensation of isatoic anhydride 27 with 2-phenethylamine (28) results in net acylation of the aliphatic amine. The anhydride is in essence both an activated carboxyl derivative and a means of protecting the aniline nitrogen against self-condensation reactions. The secondary amine in 29 is then converted to the tosylamide to protect it during subsequent steps. Treatment of the amide 30 with phosphorus pentoxide results in
Miscellaneous Fused Heterocycles

a Bischler-Napieralski cyclization to the dihydroisoquinoline 31. The protecting group is then removed by hydrolysis in strong acid (32), and the double bond is reduced catalytically. Alkylation of the diamine 33 with ethyl bromoacetate proceeds as expected at the more basic aliphatic amine to give the glycinate Base-catalyzed ring closure of the aminoester 34. serves to close the diazepine ring; there is thus obtained the anxiolytic agent clazolam (35).6



(35)

 $(32) R = p - Cl_3C_6l_4$ (33) R = 11

When the pharmacophoric group in a rigid compound is fused in some position remote from that in the nonrigid compounds, it is likely that the agent is active by some different biological mechanism. Thus, although *naranol* (40) is formally related to the tricyclic compounds, the basic center is in a quite different position from that in the majority of tricyclic CNS agents. Synthesis of 40 is begun by Mannich reaction of 2-naphthol with formaldehyde and dimethylamine to afford the adduct 37. Reaction of this aminophenol with the substituted piperidone 38 affords the tetracyclic product 40 in a single step.



C!! 3



(41)

This seemingly complex transformation can be rationalized by assuming, as the first step, formation of an enolate of ketone 38. Displacement of dimethylamine on 37 by the enolate will give the phenolketone 39. Although both regioisomers of the enolate may in fact be formed, the observed product is from reaction of the less hindered enol. (An alternate sequence involves loss of dimethylamine from 37 to give quinonemethide 41; conjugate addition of the same enolate will give 39.) Simple internal hemiketal formation gives the product 40, narano1,⁷ of unspecified stereochemistry.

Although most available CNS agents are guite effective, they are not without side effects. There is, thus, some impetus for a search for novel structures in the hope that these will be better than available drugs. During this search a derivative of a partly reduced indole, molindone (48), has been reported to have sedative and tranquilizing activity. Condensation of oximinoketone 42 (from nitrosation of 3-pentanone), with cyclohexane-1,3-dione in the presence of zinc and acetic acid leads directly to the indole derivative 47. The transformation may be rationalized by assuming as the first step, reduction of 42 to the corresponding α -aminoketone. Conjugate addition of the amine to 43 followed by elimination of hydroxide (as water) would give ene-aminoketone 44. This may be assumed to be in tautomeric equilibrium with intermediate 45. Aldol condensation of the side chain carbonyl group with the doubly activated ring methylene would then result in cyclization to

pyrrole 46; simple tautomeric transformation would then give the observed product. Mannich reaction of 47 with formaldehyde and morpholine gives the tranguilizer molindone (48).⁸



Tricyclic antihistamines as a rule carry aliphatic nitrogen as a substituent on a side chain attached to the central ring; the side chain nitrogen may be part of a heteroaromatic ring. Conjugate addition of pchloroaniline (49) to the substituted vinylpyridine 50 gives the alkylated aniline 51. Treatment of that intermediate with nitrous acid leads to N-nitroso intermediate 52 which is then reduced to the hydrazine (53). Reaction of 53 with N-methyl-4-piperidone under the conditions of the Fischer indole synthesis affords dorastine (54),⁹ an antihistamine.



Azanator (59) represents a more classical antihistaminic structure, since the more basic nitrogen in this case occurs in the side chain. Preparation



of this compound starts with aromatic nucleophilic displacement on pyridine 55 (see Chapter 14) with phenoxide anion. Friedel-Crafts ring closure of the product (56) by means of polyphosphoric acid leads to the azaxanthone 57. This is then converted to the final product by condensation with the Grignard reagent from N-methyl-4-chloropiperidine (58), followed by dehydration to yield 59.¹⁰

As noted previously, a wide variety of aromatic systems serve as nuclei for arylacetic acid antiinflammatory agents. It is thus to be expected that fused heterocycles can also serve the same function. Synthesis of one such agent (64) begins with condensation of indole-3-ethanol (60) with ethyl 3-oxocaproate (61) in the presence of tosic acid, leading directly to the pyranoindole 63. The reaction may be rationalized by assuming formation of hemiketal 62, as the first step. Cyclization of the carbonium ion



Miscellaneous Fused Heterocycles

(from loss of hydroxyl) into the nucleophilic indole 2-position will give the observed product (63). Saponification of the ester gives the antiinflammatory agent prodolic acid (64).¹¹

A closely related compound, *pirandamine* (72), bearing a basic rather than an acidic side chain and having a methylene in place of the indole nitrogen,



(<u>69</u>)



 $(\underline{71}) R = N(CH_3)_2$

interestingly exhibits antidepressant activity. Basically, the same synthetic scheme is used for the preparation of this analogue as for compound 64above. Condensation of 1-indanone (65) with ethyl bromoacetate and zinc affords Reformatski product 66; then, reduction with lithium aluminum hydride gives diol 67. Dehydration with sulfuric acid gives the indene ethanol 68. Acid catalyzed condensation of 68 with ethyl acetoacetate then gives the fused tetrahydropyran derivative 69, no doubt by a scheme quite analogous to that above. The ester is then saponified to the corresponding acid (70), which is then converted to the dimethylamide (71). Reduction with lithium aluminum hydride completes the synthesis of the antidepressant agent *pirandamine* (72).¹²

Antidepressant activity is retained in tandamine (80), an analogue in which the indole ring is restored, the basic side chain is retained, and the oxygen heterocycle is replaced by the corresponding sulfurcontaining ring. Acetylation of indole ethanol 60 affords the corresponding acetate 73; the indole nitrogen is then alkylated by means of ethyl iodide and sodium hydride (74). Conversion of the side chain oxygen to sulfur is accomplished by first treating the alcohol (from hydrolysis of the acetate (75) with phosphorus tribromide to give 76; displacement of halogen with thiosulfate anion then affords the covalent thiosulfate (77). In a departure from the synthetic scheme used above, the basic side chain is introduced directly. Thus, reaction of thiosulfate 77 with amidoketone 78 in the presence of



boron trifluoride leads directly to the fused heterocycle (79). Reduction of the formamide by means of lithium aluminum hydride then affords monomethyl derivative 80; N-methylation of that intermediate completes the synthesis of the antidepressant agent tandamine (81). 13, 14

A rather complex fused isoindoline (87) has been found to show good anorectic activity. This substance differs from other anorectic agents by not being a β -phenethylamine analogue. Preparation of this compound starts by reaction of a substituted benzoylbenzoic acid (82) with ethylene diamine. The product (84) can be rationalized as being the aminal from the initially obtained monoamide 83. This is then subjected to reduction with lithium aluminum hydride

and--without isolation--air oxidation. Reduction probably proceeds to the mixed aminal/carbinolamine 85; such a product would be expected to be in equilibrium with the alternate aminal 86. The latter would be expected to predominate due to the greater stability of aldehyde aminals over the corresponding ketone derivatives. Air oxidation of the tetrahydroimidazole to the imidazoline will then remove 86 from the equilibrium. There is thus obtained the anorectic agent mazindol (87). 15











Purines and Related Heterocycles 3. Considerable research has been devoted to preparation of modified purines in the expectation that such compounds could act as antagonists to, or possibly false substrates for, those involved in normal metabolic processes. It is surprising to note the relatively small number of such compounds that have found clinical use.









(90)

(91)

Thioguanine is one of the most familiar of the medicinal purine analogues. This compound acts as a false guanine and has found a role as an antineoplastic agent by reason of its resulting activity as a metabolic inhibitor. The compound is obtained most simply by displacement of halogen from 6-chloroguanine (88) with thiocyanate anion. Hydrolysis of the product (89) yields thioguanine (90).¹⁶

In much the same vein, displacement of chlorine from 88 with the sodium salt of imididazolethiol 91 affords the antineoplastic agent *thiampirine* (92).¹⁷ The same reaction starting with purine 93 gives the immunosupressant agent *azathioprine* (94).¹⁸

Contraction and relaxation of smooth muscle is known to be mediated by way of the cyclic nucleotides. In brief, increase in intracellular levels of cyclic adenosine monophosphate (CAMP) leads to relaxation of smooth muscle. In the normal course of events, cAMP is hydrolyzed to its inactive form by the enzyme phosphodiesterase (PDE). Drugs that inhibit the action of that enzyme--PDE inhibitors--will tend to promote smooth muscle relaxation. One such drug, theophylline (95) has found extensive use in treatment of asthma based on its ability to relax bronchial smooth muscle. A search for more lipophilic analogues of theophylline led to a compound, the hexyl analogue 96 of theobromine, which seemed to have greater selectivity for vascular smooth muscle. Further biological investigation revealed that the active agent was in fact the metabolite 101 resulting from w-l-oxidation of the aliphatic side chain.

Preparation of the requisite side chain starts by alkylation of ethyl acetoacetate with 1,3-dibromopentane; the initially formed bromoketone (shown as the enol 97) undergoes O-alkylation under the reaction conditions to give the dihydropyran 98. Reaction of that masked hydroxy ketone derivative with hydrogen



(100)

(99)

bromide affords the requisite bromoketone (99); reaction conditions are apparently sufficient to insure decarbethoxylation of the ketoester intermediate. Alkylation of theobromine (100) with 99 affords the vasodilator, pentoxifylline (101).¹⁸



Pharmacognosy, the study of plant products with medicinal properties, has contributed many structural leads to drug development. Although findings have in recent years been less frequent this discipline

continues to uncover unusual structure-activity combinations. In one example, methanol extracts of the Japanese mushroom Lentinus edodes Sing. were found to have hypolipidemic activity. The active compound eritadenine (109) proved to be a purine alkylated with an oxidized sugar fragment; its synthesis can be accomplished as follows. Ring opening of the protected lactone (102), derived from erythrose, with sodium phthalimide gives the acid 103; hydrazinolysis then leads to the amino acid 104. Displacement of chlorine in pyrimidine 105 by the amine function on 104 serves to attach the future imidazole nitrogen and the sugar-derived side chain 106. The nitro group is then reduced by catalytic hydrogenation (107), the resulting primary amine is the most basic, and is selectively formylated with formic acid. These strongly acidic conditions serve to remove the acetonide protecting group as well (108). Treatment with sodium hydroxide then serves to close the imidazole ring, forming eritadenine (109).¹⁹

The several compounds below (115, 120, 121) are related to purines only in that they contain some three nitrogen atoms formally distributed among an indene nucleus. Despite the varied structures, all three analogues share activity mediated through the CNS. In one of the classical methods for construction of a pyrimidine ring, synthesis of 115 begins with condensation of the substituted cyanoacetate 110 with acetamidine to give the corresponding pyrimidone (111), shown as the enol. Treatment with acid probably results initially in hydrolysis of the acetal function to give the transient aminoaldehyde *112*. This then cyclizes to the corresponding imine under the reaction conditions, and this interemdiate tautomerizes to the observed pyrrolopyrimidine *113*. Reaction with phosphorus oxychloride serves to replace the hydroxyl group by chlorine (*114*). Displacement of halogen with benzylamine gives the muscle relaxant rolodine (*115*).²⁰



Condensation of aminopyrazole *116* with ethoxymethylene malonic ester gives the product of additionelimination (*117*), which is then cyclized to the piperidone by heating in diphenyl ether. The product tautomerizes spontaneously to the hydroxypyridine *118*. The hydroxyl group is then converted to the chloro derivative by means of phosphorus oxychloride (*119*). Displacement of halogen by <u>n</u>-butylamine gives the antidepressant compound cartazolate (120).²¹ Replacement of halogen by the basic nitrogen of acetone hydrazone affords the antidepressant etazolate (121).²¹



4. Polyaza Fused Heterocycles

As noted earlier (see Chapter 12), considerable latitude exists in the *nalidixic acid* type antibacterial agents as to the exact nature of the two heterocyclic rings. The minimum requirement for activity seems to reside in a fused enaminoketone carboxylate function. (Even so, an additional nitrogen atom may be interposed in that function, viz. *cinoxacin.*) Consistent with this, it is interesting that inclusion of an additional nitrogen atom in the pyridino ring also gives a molecule (127) that shows antibacterial activity. Synthesis of this agent begins with successive displacement reactions on 2,6-dichloropyrimidine (122) with pyrrolidine and then ammonia, leading to the diaminopyrimidine 123. The rest of the synthesis follows the usual pattern. Condensation of 123 with ethoxymethylenemalonate gives the substituted malonate 124. Thermal cyclization serves to form the fused pyridone ring (125); saponification of the ester with base then gives the corresponding acid (126). Alkylation of the pyridone nitrogen with diethyl sulfate completes the synthesis of piromidic acid (127).²²



Replacement of methine by nitrogen, i.e., replacement of a phenyl moiety by pyridine, is consistent with biological activity in quite a few structural-

Miscellaneous Fused Heterocycles

biological classes (see Chapter 9). This retention of activity in the face of an interchange of aromatic rings is well illustrated in the case of the acyclic and tricyclic antihistamines. It is of note that the same interchange in at least one tricyclic antidepressant drug (*dibenzepin*, see Chapter 14), affords



$$(CH_3)_2NCH_2CH_2C1 \qquad (CH_3)_2N \qquad (CH_3)$$

an analogue that retains the CNS profile of the parent compound. Another centrally acting tricyclic agent bearing a pyridino moiety (132) is prepared as follows. Condensation of phenylenediamine (128) with 2-chloronicotinic acid (129) leads directly to the tricyclic lactam 130. Although the reaction obviously includes amide formation and nucleophilic aromatic displacement of chlorine, the order of these steps is

471

not known. Alkylation of the anion obtained from treatment of 130 with the chloroethylamine 131 affords the antidepressant compound propizepine (132).²³ The last step in this sequence is less straightforward than it might seem. There is considerable evidence that such alkylations often proceed by way of the aziridinium ion (133). It will be appreciated that attack of the anion at the secondary or tertiary carbon of the aziridinium ring will lead to different products. Extensive investigation of this problem²⁴ has established that the product from attack at secondary carbon usually predominates. This is, of course, the same compound that would be formed by direct displacement of halogen without involvement of the aziridnium intermediate 133.

Two rather broad structural classes account for the large majority of drugs that have proven useful in the clinic for treating depression. Each of these has associated with it some clearly recognized side effects: the monoamine oxidase inhibitors, most commonly derivatives of hydrazine, tend to have undesirable effects on blood pressure; the tricyclic compounds on the other hand may cause undesirable changes in the heart. Considerable effort has thus been expended toward the development of antidepressants that fall outside those structural classes. An unstated assumption in this work is the belief that very different structures will be associated with a novel mechanism of action and a different set of ancillary activities. One such compound, trazodone

Miscellaneous Fused Heterocycles

 $(1\underline{38})$, has in fact shown clinically useful antidepressant activity without the typical side effects of the classical drugs. In a convergent synthesis, reaction of 2-chloropyridine with semicarbazide in the presence of a catalytic amount of acid affords the fused triazole 135. The reaction may be rationalized by assuming addition of semicarbazide to the protonated atom of chloropyridine to give intermediate 134. (Although semicarbazide is a stronger base, protonation of that compound does not lead to any reaction.) Elimination of hydrogen chloride







restores aromaticity, and leads to attack by the pyridine nitrogen on the semicarbazide carbonyl. This or the reverse order will give the observed product (135). Alkylation of piperazine 136 with 1bromo-3-chloropropane gives the piperazine derivative 137; use of that intermediate to alkylate heterocycle 135 affords the antidepressant agent trazodone (138).²⁵

A fused heterocyclic compound (146) distantly related to the antiinflammatory agent *cintazone* (Chapter 12), which itself can be viewed as a cyclized derivative of *phenylbutazone*, retains the activity of the prototype. In the synthesis of 146, reaction of the nitroaniline 139 with phosgene gives intermediate 140, which is then reacted with ammonia to afford the substituted urea (141). Cyclization of the <u>ortho</u> nitrourea function by means of sodium hydroxide leads to the N-oxide (142); this last reaction represents



474

one of a series of transformations in which nitro and nitroso groups reveal electrophilic character akin to carbonyl groups. Reaction of 142 with phosphorous oxychloride serves to convert the hydroxyl group to chloride (143), which is then displaced with dimethylamine to give the key intermediate 144.²⁷ Catalytic reduction then converts the azoxide function to the corresponding cyclic hydrazine derivative (145). Finally, condensation with diethyl <u>n</u>-propylmalonate affords the antiinflammatory agent, apazone (146).²⁸

5. Ergolines

Ergotism, popularly known at the time as "St. Anthony's Fire," was one of the dread epidemic diseases of the Middle Ages. Its victims suffered gangrenous degeneration, madness, and death. Scientific investigation eventually revealed that this disease was due to ingestion of foods prepared from rye which was infected with a fungus, *Claviceps purpurea*. These infected foods were more likely to be ingested in times of famine, so prevention of ergotism in modern times is a simple matter. Chemical investigation of *Claviceps purpurea* revealed mycotoxins that were amides of *lysergic acid (147)*, involving a series of unusual internally cyclized tripeptides.

Some of these natural products--and drugs made from them--are known collectively as the ergot alkaloids, and have found use in medicine. *Ergonovine*, for example, is a selective stimulant for contraction of uterine muscle and is used in conjunction with labor and delivery. A mixture of hydrogenated ergot alkaloids--reduced at the 9,10-position--has found use as a cerebral vasodilator by reason of its α -adrenergic blocking activity.

Lysergic acid itself has been used as starting material for a small series of drugs. This natural product was until quite recently difficultly accessible because *Claviceps* molds could only be cultivated on growing grains and grasses. Once harvested, the mixture of ergot alkaloids needed to be subjected to alkaline hydrolysis to yield the free acid. The search for a more efficient method of production led to the finding of a related mold, *Claviceps paspali*, which can be grown in submerged culture in fermentation tanks; this method of culture is additionally advantageous, as it affords the acid directly, thus bypassing the hydrolysis step.²⁸

The discovery of the potent hallucinogen LSD-25 (148), (or in street parlance, "acid"), represents one of the classics in serendipity. In the course of an analogue program on lysergic acid derivatives in the Sandoz laboratories in Switzerland, Hoffman had occasion to prepare the simple diethylamide derivative. On his way home from work that day, he saw the city of Basle in an entirely new light. The fantastic potency of the compound had led him to ingest sufficient drug as dust to experience the hallucinogenic Recognizing the probable cause of his "trip," effect. he verified the effect by deliberately taking a second dose. This is one of those interesting cases where animal pharmacology and toxicology came after the human trial.

476

A number of hallucinogens, including LSD-25, enjoyed considerable vogue in the counterculture of the late nineteen sixties. Since there exists no legitimate source for the drug (it has no recognized clinical use), underground laboratories no doubt broadened their repertoire from acetylation of morphine (to produce heroin) to include amide formation from lysergic acid. (The reaction goes particularly well in dimethylformamide; for some years a major manufacturer of this solvent showed this reaction in its advertisements to illustrate the versatility of their products!) Lysergic acid has been prepared by total synthesis by a group at Lilly²⁹; rumor has it that some of the illicit LSD was racemic, and thus a product of underground total synthesis. If so, this reflects a considerable and unexpected degree of expertise!

Migraine is a particularly virulent form of headache of which that suffered by the majority of mankind is but a pale reflection; the common remedies, such as aspirin, are all but useless against these attacks. Although the exact etiology of migraine is not known, an attack does involve at one stage dilation of the cerebral vasculature. The skull is a bony case that cannot accommodate volume expansion of any magnitude. *Methysergide* (152), a lysergic acid derivative, which acts as a cerebral vasoconstrictor, has proven of use in treatment of migraine. Alkylation of methyl lysergate (149) with methyl iodide, by means of the anion formed with potassium amide, gives the N-methylated product (150). This is then saponified (to 151) and converted to the amide with 2-amino-l-butanol. There is thus obtained methysergide (152).³⁰



A different substitution pattern leads to 157, a molecule that exhibits peripheral α -adrenergic blocking activity. This is manifested as vasodilating activity. Photochemical addition of methanol to the 9,10-double bond of acid 151 affords the methyl ether with the trans ring fusion (153).³¹ Reduction of the corresponding ethyl ester (154) with lithium aluminum hydride then gives the carbinol 155. Esterification of that alcohol with substituted nicotinic acid 156, gives the vasodilator nicergoline (157).³²



Yet different elaboration of the same molecule affords a compound (162) that acts as an inhibitor to the pituitary peptide hormone prolactin, the factor responsible for supporting lactation. As such the drug has found use in suppressing lactation and in the treatment of prolactin-dependent breast tumors. In the synthesis of 162, catalytic hydrogenation of lysergic acid proceeds from the less hindered side of the molecule to afford the derivative with the <u>trans</u> ring junction (158).³⁰ As above, reduction of the methyl ester (159) gives the corresponding carbinol. This is then converted to the methane sulfonate (160), and that function is displaced with cyanide ion to afford the acetonitrile derivative 161.



Chlorination with N-chlorosuccinimide at the activated indole 2-position gives the corresponding chloro derivative, the prolactin inhibitor *legotrile* (*162*).³³

REFERENCES

- Anon., Netherlands Application 6,606,390 (1967); Chem. Abstr., 66: 55535 (1967).
- A. D. Miller, U. S. Patent 3,975,532 (1976); Chem. Abstr., 85: 177393m (1976).
- T. Henshall and E. W. Parnell, J. Chem. Soc., 661 (1962).
- 4. H. Hermans, K. F. Hubert, G. A. Knaeps and J. J.
 M. Willems, U. S. Patent 3,679,686 (1972); Chem.
 Abstr., 78: 43295 (1972).
- W. J. Van Der Burg, I. L. Bouta, J. De Lobelle,
 C. Ramon and B. V. Vargaftig, J. Med. Chem., 13, 35 (1970).
- H. Otto, British Patent 1,113,754 (1969); Chem. Abstr., 70: 78031 (1969).
- 7. M. Von Strandtmann, M. P. Cohen and J. Shavel, U. S. Patent 3,549,641 (1970); Chem. Abstr., 75: 91297 (1971).
- Anon., Belgian Patent 670,798 (1966); Chem. Abstr., 65: 7148 (1966).
- 9. L. Berger and A. J. Coraz, U. S. Patent 3,409,628 (1968); Chem. Abstr., 71: 38939 (1969).
- F. J. Villani, T. A. Mann, A. E. Wefer, J. Hannon, L. L. Carca, M. J. Landon, W. Spivak, D.

Vashi, S. Tuzzi, G. Danks, M. del Prado and R. Lutz, J. Med. Chem., 18, 1 (1975).

- C. A. Demerson, L. G. Humber, T. A. Dobson and R. R. Martel, J. Med. Chem., 18, 189 (1975).
- I. Jirkovsky, L. G. Humber and R. Noureldin, Eur. J. Med. Chem., 11, 571 (1976).
- I. Jirkovsky, L. G. Humber and R. Noureldin, J. Heterocyclic Chem., 12, 937 (1975).
- I. Jirkovsky, L. G. Humber, K. Voitw and M. P. Charest, Arzneimittelforsch., 27, 1642 (1977).
- P. Aeberli, P. Eden, J. H. Gogerty, W. J. Houlihan and P. Penberthy, J. Med. Chem., 18, 177 (1975).
- 16. G. H. Hitchings, G. B. Elison and L. E. Mackay,
 U. S. Patent 3,019,224 (1962); Chem. Abstr., 58:
 3443a (1963).
- G. H. Hitchings and G. B. Elison, U. S. Patent
 3,056,785 (1962); Chem. Abstr., 58: 5701 (1963).
- W. Mohler and A. Soder, Arzneimittelforsch., 21, 1159 (1971).
- T. Kamiya, Y. Saito, M. Hashimoto and H. Seki, Tetrahedron Lett., 4729 (1969).
- R. A. West and L. Beauchamp, J. Org. Chem., 26, 3809 (1961).
- 21. H. Hoehn and T. Deuzel, German Patent 2,123,318 (1971); Chem. Abstr., 76: 59619 (1971).
- 22. S. Minami, T. Shono and J. Matsumoto, Chem. Pharm. Bull., 19, 1426 (1971).
- C. Hoffmann and A. Faure, Bull. Soc. Chim. Fr., 2316 (1966).

- 24. See for example, D. Lednicer and L. A. Mitscher, Organic Chemistry of Drug Synthesis, Vol. 1, p. 79, 374 (1975).
- G. Palazzo and B. Silverstrini, U. S. Patent
 3,381,009 (1968); Chem. Abstr., 69: 52144 (1968).
- 26. F. J. Wolf, R. M. Wilson, K. Pfister and M. Tischler, J. Amer. Chem. Soc., 76, 4611 (1954).
- 27. G. Mixich, Helv. Chim. Acta, 51, 532 (1968).
- 28. A. Stoll and A. Hoffmann, "Chemistry of the Alkaloids," S. W. Pelletier, ed., Von Nostrand, Reinhold and Company, New York, New York, 1970, pp. 267-300.
- 29. E. D. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, R. G. Jones and R. B. Woodward, J. Amer. Chem. Soc., 76, 5226 (1954); E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones and R. B. Woodward, J. Amer. Chem. Soc., 78, 3087 (1956).
- 30. Anon., British Patent 811,964 (1959); Chem. Abstr., 53: 18969 (1959).
- W. Barbieri, L. Bernardi, G. Bosiosi and A. Temperilli, *Tetrahedron*, 25, 2401 (1969).
- 32. G. Acari, L. Bernardi, G. Bosiosio, S. Coda,
 G. B. Freguan and A. H. Glaser, *Experientia*, 28, 819 (1972).
- 33. J. A. Kornfeld and N. J. Bach, German Patent 2,335,750 (1974); Chem. Abstr., 80: 146400 (1974).

Indexes

Cross Index of Drugs

Adrenal Suppressant

Trilostane

Adrenergic Agents

Adrenalone Amidephrine Clorprenaline Deterenol Domazoline Esproquin Etafedrine Metizoline Soterenol

a-Adrenergic Blocking Agents

Fenspiride

 β -Adrenergic Blocking Agents

Acebutolol	Metoprolol
Atenolol	Moprolol
Bufuralol	Nadolol
Bunitridine	Oxprenolol
Bunitrolol	Phenbutalol
Bunolol	Pindolol
Metalol	Practolol
Bufuralol Bunitridine Bunitrolol Bunolol Metalol	Nadolol Oxprenolol Phenbutalo Pindolol Practolol

 β -Adrenergic Blocking Agents (cont.)

SotalolTiprenololTazololTolamololTimololTolamolol

Aldosterone Antagonists

Canrenoate		Mexrenoate,	Potassium
Canrenone,	Potassium	Prorenoate,	Potassium

Anabolic Steroids

Bolandiol Diacetate	Norbolethone
Bolasterone	Quinbolone
Boldenone	Stenbolone Acetate
Bolmantalate	Tibolone
Mibolerone	

Analgesics

Anidoxime	Molinazone
Anileridine	Nalbuphine
Anilopam	Nalmexone
Benzydamine	Naltrexone
Buprenorphine	Nefopam
Butacetin	Nexeridine
Butorphanol	Noracymethadol
Carbiphene	Octazamide
Clonixeril	Oxilorphan
Clonixin	Proxazole
Dimefadane	Pyrroliphene
Dipyrone	Salsalate
Etorphine	Tetrydamine
Ketazocine	Tramadol
Letimide	Volazocine
Methopholine	Xylazine
Mimbane	-

Anesthetics

Etoxadrol Propanidid Tiletamine

Anorexic Agents

Aminorex Amphecloral Clominorex Fenisorex		Fludorex Fluminorex Mazindol Mefenorex
Anterior	Pituitary	Activator
Epimestrol		
Anterior	Pituitary	Suppressant

Danazol

Antiadrenal

Trilostane

Antiadrenergics

Solypertine

Zolterine

Antiamebics

Bialamicol Clamoxyquin Symetine Teclozan

Antiandrogens

Benorterone Cyproterone Acetate Delmadinone Acetate

Antianginals

Flunarizine

Nifedipine

Antiarrhythmic Agents

Amoproxan Aprindine Bucainide Bunaftine Capobenic Acid Disopyramide Pirolazamide Pranolium Chloride Pyrinoline Quindonium Bromide Rodocaine

Antibacterials

Acedapsone
Acediasulfon e
Acetosulfone Sodium
Biphenamine
Carbadox
Cinoxacin
Diaveridine
Mafenide
Mequidox
Nifuratrone
Nifurdazil
Nifurimide
Nifuroxime
Nifurpirinol

Antibiotics

Amicycline Cefadroxil Cefadroxil Cefazolin Cefoxitin Cephacetrile Cephapirin Cephradine Cetophenicol Clavulanic Acid Cyclacillin Nifurquinazol Nifurthiazole Nitrofuratrone Ormetoprim Oxolinic Acid Phenyl Aminosalicylate Piromidic Acid Racephenicol Sulfabenzamide Sulfacytine Sulfanitran Sulfasalazine Sulfazamet Thiamphenicol

Democycline Meclocycline Methacycline Nitrocycline Nocarcidins Sancycline Talampicillin Thienamycin Thiphencillin Ticarcillin

Anticholinergic Agents

Alverine	
Benapryzine	
Benzetimide	
Benzilonium	Bromide

Butropium Dexetimide Domazoline Elantrine Elucaine Glycopyrrolate Heteronium Bromide Oxybutynin Oxyphencyclimine Parapenzolate Bromide Pentapiperium Methylsulfate Phencarbamide Poldine Methylsulfate Proglumide Propenzolate Thiphenamil Tofenacin Triampyzine
Anticoagulant

Bromindione

Anticonvulsants

Albutoin	Eterobarb
Atolide	Sulthiame
Citenamide	Tiletamine
Cyheptamide	

Antidepressants

Aletamine	Intriptvline
Amedalin	Isocarboxazid
Amovanine	Ketinramine
	Manastilina
Bubropion	Maprotifine
Butacetin	Melitracin
Cartazolate	Mianserin
Clodazon	Modaline
Cotinine	Octriptyline
Cypenamine	Oxypertine
Cyprolidol	Pirandamine
Cyproximide	Pizotyline
Daledalin	Propizepine
Dazadrol	Quipazine
Dibenzepin	Rolicyprine
Dioxadrol	Sulpiride
Encyprate	Tandamine
Fantridone	Thiazesim
Fenmetozole	Thozalinone
Gamfexine	Trazodone
Guanoxyfen	Viloxazine
Hepzidine	

Antiemetics

Metopimazine

Trimethobenzamide

Antiestrogens

Clometherone Delmadinone Acetate Tamoxifen

Antifungals

Biphenamine	Miconazole	
Ciclopirox	Tolindate	
Econazole	Tolnaftate	
Ethonam		

Antihelmintics

closamide
tramisole
trodan
antel
fendazole
ibendazole
enium Closylate

Antihistaminics

Azanator	Dorastine
Azatadine	Mianserin
Clemastine	Rotoxamine
Closiramine	Terfenadine

Antihypertensives

Aceperone	
Alipamide	
Amquinsin	
Bupicomide	
Chlorothiazide	
Clopamide	
Diapamide	
Guanabenz	
Guanisoquin	
Guanochlor	
Guanoxabenz	
Guanoxyfen	

Hydracarbazine Indoramine Leniquinsin Methyldopa Metolazone Mexrenone Pazoxide Prazocin Quinazocin Trimoxamine Trimazocin

Antiinflammatory Steroids

Amcinafal	
Amcinafide	
Cormethasone	Acetate
Cortivazol	

Desonide Difluprednate Drocinonide Endrysone Antiinflammatory Steroids (cont.)

Flunisolide Halcinonide Nivazol Tralonide Triclonide

Antimalarials

Amquinate

Menoctone

Antimigrane

Methysergide

Antineoplastics

Azathioprine Azatepa BCNU Benzodepa Calusterone CCNU Dacarbazine Lomustine MeCCNU Melphalan Oxisuran Pipobroman Piposulfan Procarbazine Semustine Tamoxifen Testolactone Thiampirine Thioguanine

Antiparkinsonism Agents

Carbidopa Carmantadine Dopamantine Lometraline

Antiperistaltics

Alkofanone Difenoximide Difenoxin Fetoxylate Fluperamide Loperamide

Antiprotozoals

Carnidazole	Nimorazole
Flubendazole	Nithiazole
Flunidazole	Oxamniquine
Ipronidazole	Ronidazole
Moxnidazole	Sulnidazole
Nifursemizone	

Antipyretics

Benzydamine Dipyrone

Antipsychotics

Carpipramine

Antischistosomals

Becanthone Niridazole Indoxole

Clocapramine

Oxamniquine Teroxalene

Antispasmodic Agents

Butamirate

Carmantadine

Antitrichomonals

Nimorazole

Antitussives

Amicibone Benproperine Butamirate

Clobutinol Codoxime Pemerid

Antivirals

Amantadine Famotine Memotine

Methisazone Rimantadine Tilorone

Avian Chemosterilant

Azacosterol

Bronchodilators

Albuterol*	Fenspiride
Carbuterol*	Hoquizil
Clorprenaline*	Isoetharine*
Doxaprost	Piquizil
Eprozinol	Pirbuterol*
Fenoterol*	Prostalene

Bronchodilators (cont.)

Quazodine	Sulfonterol*
Quinterenol*	Suloxifen
R̃imiterol *	Trimethoguinol*
Soterenol*	_
*adrenergic	

CNS Stimulants

Amphetaminil Ampyzine Azabon Difluanine Ethamivan Flubanilate Indriline Mefexamide Pyrovalerone Trazodone

Canine Contraceptive

Mibolerone

Cardiotonics

Benfurodil

Dobutamine

Catecholamine Potentiator

Talopram

Cathartics

Bisoxatin Acetate

Oxyphenisatin Acetate

Choleretic

Piprozolin

Cholinergic Agent

Aceclidine

Coccidiostats

Alkomide	Proquinolate
Cyproquinate	Sulfanitran
Decoquinate	Triazuril
Neguinate	

Coronary Vasodilators

Dobutamine	
Flunarizine	
Medibazine	
Mixidine	

Corticoids

Cloprednol Drocinonide Flunisolide Halcinonide

Furosemide

Indapamide

Metalazone

Prorenone

Triflocin

Xipramide

Fenestrol

Nylestriol

Ticrynafen

Methalthiazide

Nifedipine Oxprenolol Oxyfedrine Terodiline

Cough Suppressant

Amicibone

Diuretics

Alipamide Ambuside Azolimine Bumetanide Chlorothiazide Clazolimine Clopamide Clorexalone Diapamide

Estrogens

Epimestrol Estrazinol Estrofurate

Estrus Regulators

Cloprostenol Fluprostenol Prostalene

Expectorant

Bromhexine

Fibrinolytic

Bisobrin

Gastric Antisecretory Cimetidine Metiamide Tiquinamide Deprostil Glucocorticoids Clocortolone Acetate Flurandrenolide Cortivazol Formocortal Descinolone Acetonide Medrysone Diflucortolone Nivazol Prednival Flucloronide Fluperolone Acetate Hemostatics Aminomethylbenzoic Acid Tranexamic Acid Hypoglycemic Isobuzole Hypolipidemics Beloxamide Nafenopin Pimetine Boxidine Clofenpyride Probucol Eritadenine Tibric Acid Halofenate Treloxinate Lifibrate Hypotensives

Amquinsin Pror**e**none Prostalene

Immunosuppressant

Azathioprine

Interferon Inducer

Tilerone

Local Anesthetics

Amoproxan Biphenamine Diamocaine Dexivacaine

Luteolytic Agents

Cloprostenol

Fluprostenol

Etidocaine

Risocaine

Rodocaine

Mucolytic

Bromhexine

Muscle Relaxants

Baclofen Benzoctamine Cinnamedrine Dantrolene Fenalamide Fenyripol Fetoxylate Flavoxate Fletazepam Flumetramide Isomylamine Lorbamate Mebeverine Mesuprine Metaxalone Nafomine Pancuronium Bromide Prazepam Proxazole Ritodrine Rolodine Methixine Xylazine

Narcotic Antagonists

Nalbuphine Nalmexone Naltrexone

Narcotics

Anileridine Buprenorphine Butorphanol Etorphine Oxilorphan

Non-Steroidal Antiinflammatory Agents

Alclofenac Apazone Bendazac Benoxaprofen Benzydamine Cicloprofen Non-Steroidal Antiinflammatory Agents (cont.)

Cintazone Cliprofen Clonixeril Clonixin Clopirac Diclofenac Diflumidone Diflunisal Etoclofene Fenamole Fenbufen Fenclorac Fenclozic Acid Fenoprofen Fenoterol Fenpipalone Flazolone Flufenamic Acid Flumizole Flunisolide Flunixin Flutiazin Furobufen

Indoxole Intrazole Isoxicam Ketoprofen Meclofenamic Acid Nimazone Oxaprozin Paranyline Pirprofen Prodolic Acid Proquazone Proxazole Pyroxicam Salsalate Sudoxicam Sulindac Suprofen Tesicam Tesimide Tetrydamine Tolmetin Triflumidate

Oral Hypoglycemics

Glyoctamide
Glyparamide
Metformin
Tolpyrramide

Pituitary Suppressant

Danazol

Progestins

Algestone Acetonide Algestone Acetophenide Angesterone Acetate Cingestol Clogestone Clomegestone Acetate Delmadinone Acetate Dexnorgestrel Acetime Ethynerone Flurogestone Acetate Gestaclone Gestonorone Progestins (cont.)

Haloprogesterone Medrogestone Methynodiol Diacetate Norgestomet Tigestol

Prolactin Inhibitor

Lergotrile

Respiratory Stimulants

Dimefline

Doxapram

Sedatives

Benzoctamin**e** Clozapine Midaflur Alonimid Flunitrazepam Nisobamate Nisobamate Tricetamide Trimetozine Perlapine Roletamide

Sedatives - Tranquilizers

Acepromazine Alpertine Azaperone Benperidol Benzindopyrine Bromperidol Buspirone Butaclamol Butaperazine Carpipramine Cinperene Cintriamide Clazolam Clobazam Clocapramine Clomacran Cloperidone Clopimozide Clothiapine Clothixamide Cyclophenazine Cyprazepam Cyproximide Demoxepam Etazolate Fenimide Fletazepam Fluspiperone Fluspiriline Halazepam Hydroxyphenamate Imidoline Lenperone Lometraline Loxapine Metiapine Milipertine Molindone Naranol Nisobamate Oxiperomide Penfluridol

Sedatives - Tranquilizers (cont.)

Pimozide	Taclamine
Pinoxepin	Temazepam
Pipamperone	Thiothixene
Pipotiazine	Triflubazam
Prazepam	Tybamate
Spirilene	Uldazepam
Sulazepam	

Serotonin Inhibitors

Chlorophenylalanine	Fonazine
Cinanserin	Mianserin
Fenclonine	Xylamidine

Thyromimetic

Thyromedan

Uricosurics

Benzobromarone

Vasoconstrictors

Ciclafrine

Methysergide

Halofenate

Vasodilators

Aceperone	
Bamethan	
Benfurodil	
Betahistine	
Cin e pazide	
Flunarizine	
Hexobendine	
Ifenprodil	

Isoxsuprine Mesuprine Nafronyl Nicergoline Oxprenolol Pentoxifylline Pindolol Zolterine

Index

Acebutolol, 109 Aceclidine, 295 Acedapsone, 112 Aceperone, 332 Acetaminophen, 63 Acetanilide, 97 Acetylcholine, 71, 93, 97, 294 Acetylenes, hydration, 20 "Acid", 476 Additive effects of substituents, 179 Adrenalin, 38 Adrenalone, 38 Adrenergic agents, 36, 37 Adrenergic agonists, SAR, 37, 38, 251 Adrenergic antagonists, 105-109 β-Adrenergic antagonists, actions, 107 Adrenergic transmission, 100 Adrenergic transmitters, SAR, 106

Albendazole, 353 Albuterol, 43 Albutoin, 261 Alclofenac, 68 Aldosterone, 173 Aletamine, 48 Algestone acetonide, 171 Algestone acetophenide, 171 Alipamide, 94 Alonimid, 295 Alpertine, 342 Alphaprodine, 328 Alverine, 55 Amantadine, 18 Ambuside, 116 Amcinafal, 185 Amcinafide, 185 Amedalin, 348 Amicibone, ll Amicycline, 228 Amidephrine, 41 Aminals, 258, 462 *p-Aminob*enzoic acid, 9 7-Aminocephalosporanic acid (7ACA), 441

7-Aminodesacetylcephalosporanic acid (7ADCA), 439 α -Aminonitrile, 289 Aminooxazoline synthesis, 264 6-Aminopenicillanic acid (6APA), 437 Aminopyrine, 262 Aminorex, 265 Amiquinsin, 363 Amoproxan, 91 Amoxapine, 428 Amphecloral, 48 Amphetamine, 47 Amphetaminil, 48 Ampicillin, 437, 438 Ampyzine, 298 Amquinate, 370 Anagram, 235 Anesthetic, injectable, 15 Angesterone acetate, 165 Anidoxime, 125 Antagonists, β -adrenergic, 41 to histamine, 251 Anticholinergic activity, 71, 221 Antidepressant, 31 Antidepressant activity, 7 Antipyrine, 63, 261 Antisecretory, gastric, 3, 4 Antisecretory activity, 2 Antitussive, 11 Antiulcer activity, 2 Apazone, 475 Aphrodisiac, reputed, 347 Appetite depressants, 47 Aprindine, 208 Arbuzov reaction, 420 Aromatization, by loss of methyl group, 147, 149 Arrhythmias, cardiac, 33 Aspirin, 63, 89 Atenolol, 109

Atropine, 71 Autonomic nervous system, 36 Azabon, 115 Azacosterol, 161 Azanator, 457 Azaperone, 300 Azaphilone, 282, 296 Azatadine, 424 Azathioprine, 464 Aziridinium ion, 11, 208, 219, 325, 472 regiochemistry, 59 Aziridinium salt, 72 Azolimine, 260 *Baclofen,* 121 Bamethan, 39 BAS, 96 BCNU, 12 Becanthone, 413 Beckett-Casey rule, 328 Beloxamide, 56 Benapryzine, 74 Bendazac, 351 Benfurodil, 355, 356 *Benorteron*e, 156 *Benoxaprofen,* 356 Benperidol, 290 Benproperine, 100 Benzbromarone, 354 Benzetimide, 293 Benzilate esters, 74 Benzilonium bromide, 72 Benzindopyrine, 343 *Benzoctamine, 220* Benzodepa, 122 Benzothiadiazines, 383 Benztriamide, 290 Benzydamine, 350 Betahistine, 279 Bioisosterism (see also biological isosterism), 278 Biological isosterism, 233 Birch reduction, 145, 147,

152, 440 1,3-Biscarbamates, 21 Bischler-Napieralski cyclodehydration, 140, 377, 404, 427, 453 reaction, 224 Bismethylenedioxy protecting group, 190 β -Blockers, 41 Blood-brain barrier, 52, 213 Bolandiol diacetate, 143 Bolasterone, 154 Boldenone 10-undecylenate, 153 *Bolmantalate*, 143 Boxidine, 99 Breakthroughs, therapeutic, 446 Bromindione, 210 Bromperidol, 331 Bromhexine, 96 Bromoxanide, 94 Bronchodilator, 3, 5, 38, 45, 108 *Bucainide*, 125 Bucloxic acid, 126 Buformin, 21 Bufuralol, 110 Bumetanide, 87 Bunaftine, 211 Bunamidine, 212 Bunitridine, 215 Bunitrolo1, 106, 110 *Bun*o*lo1*, 110, 215 Bupicomide, 280 Buprenorphine, 321 Bupropion, 124 Burimamide, 251 Buspirone, 300 Butacetin, 95 *Butamirate,* 76 Butaclamol, 226 Butorphanol, 325 Butropium bromide, 308

Calusterone, 154 *Cambendazole*, 353 c-AMP, 464 *Canrenone*, 174 Carpipramine, 416 Capobenic acid, 94 Carbadox, 390 *Carbencillin,* 437 Carbidopa, 119 Carbinoxamine, 32 *Carbiphene*, 78 Carboxylation of phenols, 86 *Carbuter*ol, 41 Cardiotonic agent, 53 *Carisoprodol*, 21 Carmantadine, 20 *Carmustine*, 12 Carnidazole, 245 *Cartazolate,* 469 CCNU, 12 Cefadroxil, 440 Cefamandole, 441 *Cefazolin,* 442 Cefoxitin, 435, 443 Cephalexin, 439 Cephamycin C, 442 *Cephradine*, 440 Cephapirin, 441 Cetophenicol, 46 Chloramphenicol, 28, 45 Chlordiazepoxide, 401 Chlormadinone acetate, 165 p-Chlorophenylalanine, 52 Chlorothiazide, 395 Chlorpromazine, 409 Cholinergic transmission, 71 Cholinesterase, 294 Chromone synthesis, 391 *Ciclafrine*, 266 Ciclopirox, 282 Cicloprofen, 217 Cimetidine, 253 Cinanserin, 96 *Cinepazide*, 301

Cingestol, 145 Cinnamedrine, 39 Cinnoline synthesis, 387, 394 Cinoxacin, 388 Cintazone, 388, 474 Cintriamide, 121 Citenamide, 221 Clamoxyquin, 362 Clavulanic acid, 435 Clazolam, 452, 453 *Clazolimine*, 260 Clemastine, 32 Clioxanide, 94 Cliprofen, 65 Clobazam, 406 Clobutinol, 121 Clocapramine, 416 Clocortolone, 193 Clodazon, 354 Clofenpyride, 101 Clofibrate, 79, 101, 432 Clogestone, 166 Clomacran, 414 Clomegestone acetate, 170 Clometherone, 170 Clomifene, 127 Clominorex, 265 Clonixeril, 281 Clonixin, 281 Clopamide, 93 Cloperidone, 387 *Clopimozide,* 300 Clopirac, 235 Cloprednol, 182 Cloprostenol, 6 Clorprenaline, 39 *Closiramine,* 424 *Clothiapine*, 429 *Clothixamide*, 412 Codeine, 317 Codoxime, 318 Conjugate addition, 2, 72, 123, 140, 144, 147, 154, 175, 220, 237, 343, 412, 450, 455, 456

Corey lactol, 4 Cormethasone acetate, 194 Cormethasone acetate, 196 Cortisone, 176, 179 *Cortivazol,* 191 Cotinine, 235 *Curar*e, 162 *Cuclacillin,* **43**9 Cyclazocine, 327 Cyclic adenosine monophosphate, see cAMP Cyclobendazole, 353 Cyclopropanation, 32, 166, 168, 174. 223, 297 *Cyheptamide*, 222 Cypenamine, 7 Cyprazepam, 402 Cyprolidol, 31 Cyproquinate, 368 *Cyproterone acetate*, 166 Cyproximide, 293 Dacarbazine, 254 Daledalin, 348 Danazo1, 157 Dantrolene, 242 Dapsone, 112 Darzens condensation, 374 Dazadrol, 257 Debrisoquin, 374 Decoquinate, 368 Dehydrogenation, with chloranil, 144, 147, 170, 182, 190 with DDQ, 147, 191 microbiological, 189, 192, 196 with selenium dioxide, 160, 166, 179 Demoxepam, 401 Deprostil, 3 Descinolone, 187 Descinolone acetonide, 187, 189 Desonide, 179 Deternol, 39

Dexivacaine, 95 Dexnorgestrel acetime, 152 Diabetes, 116 Diamocaine, 336 Diapamide, 93 Diaveridine, 302 Diazepam, 452 Diazoxide, 395 *Dibenzepin,* 424, 471 Dichloroisoproterenol, 106 Diclofenac, 70 Dicyanamide, 21 Dieckmann cyclization, 72 Difenoximide, 331 Difenoxin, 331 *Diflucortolone*, 192 *Diflumidone,* 98 *Diflunisal*, 85, 86 Difluoromethylene groups, from ketones, 196 *Difluprednate*, 191 Dihydrocodeinone, 318 Dihydropyridine synthesis, 283 Dihydroxyphenylalanine, see DOPA Dimefadane, 210 Dimefline, 391 Dioxadrol, 285 Diphenoxylate, 331 1,3-Dipolar addition, 301 Dipyrone, 262 Disopyramide, 81 DNA, 12 Dobutamine, 53 Doisynolic acid, 9 Domazoline, 256 DOPA, 52, 119 Dopamantine, 52 Dopamine, 51 Dorastine, 457 Doxapram, 236, 237 Doxaprost, 3 Drocinonide, 186 Econazole, 249

Elantrine, 418 Elucaine, 44 Encyprate, 27 Endorphins, 317 Endrysone, 200 Enkephalins, 316 Ephedrine, 39 Epimestrol, 13 Epinephrine, 38, 105 Eprozinol, 44 Ergonovine, 475 Ergotism, 475 Eritadenine, 467 Eschweiler-Clark methylation, 29, 162, 210, 28{ Esproquin, 373 Estradiol, 136 Estrazinol, 142 Estriols, 138 Estrofurate, 137 Estrogenic activity, 9 Estrogens, 137 *Estron*e, 137 Estrus synchronization, 6, 183 **Etafedrine, 3**9 Etazolate, 469 Eterobarb, 304 Ethacrynic acid, 103 Ethamivan, 94 Ethonam, 249 Ethynerone, 146 Etidocaine, 95 Etoclofene, 89 Etorphine, 321 Etoxadrol, 285 False substrates, 161 Famotine, 37 Fantridone, 421 Fenalamide, 81 Fenbufen, 126 Fenclorac, 66 Fenclozic acid, 269 Fenestrel, 9 Fenimide, 237

Fenisorex, 391 Fenmetozole, 257 Fenoprofen, 67 Fenpipalone, 293 Fenoterol, 38 Fenspiride, 291 Fenyripol, 40 Fetoxylate, 331 Fibrinolysis, 8 Fire, St. Anthony's, 475 Fischer indole synthesis, 340, 457 Flavoxate, 392 Flazalone, 337 Fletazepam, 403 *Flubanilate,* 98 Flubendazole, 354 *Flucloronide*, 198 Fludorex, 44 Flufenamic acid, 69 *Fludrocortide*, 198 Flumetramide, 306 Fluminorex, 265 *Flumiz*ole, 254 *Flunarizin*e, 31 Flunidazole, 246 *Flunisolid*e, 181 Flunitrazepam, 406 Flunixin, 281 Fluperamide, 334 Fluperolone acetate, 185 Fluprostenol, 6 *Flurandrenolide*, 180 Flurogestone acetate, 183 *Fluspiperone*, 292 *Fluspirilene,* 292 *Flutiazin,* 431 Food and Drug Administration, 447 Formocortal, 189 Friedel-Crafts cyanation, 212 *Furobufen*, 416 *Furosemide*, 87 Fusaric acid, 279

*Gamfexin*e, 56 Ganglion blocking agent, 287 Gestaclone, 169 Gestonorone caproate, 152 Gliamilide, 286 *Glibornuride*, 117 Glipizide, 117 Glucocorticoids, 177 *Glyoctamide,* 117 Glyoxals, from methylketones, 42 *Glyparamide*, 117 Grewe synthesis, 327 Guanabenz, 123 *Guanethidine*, 100 Guanisoquin, 375 Guanochlor, 101 Guanoxabenz, 123 Guanoxyfen, 101 *Halcinonide*, 187 Halofenate, 80, 102 Haloform reaction, 88 Haloprogesterone, 173 Hepzidin**e**, 222 Heroin, 315 Heteronium bromide, 72 Heterosteroids, 139-142 *Hexobendine,* 92 Histamine, antagonists, 250 H₁ and H₂ receptors, 251 in ulcer² formation, 251 Hoquizil, 381 Hycanthone, 413 Hydantoin synthesis, 261 *Hydracarbazin*e, 305 Hydroxylamine-<u>o</u>-sulfonic acid, 7 Hydroxylation, osmium tetroxide, 138 Hypoglycemics, oral, 20 Hypotensive agent, 5 Ibuprofen, 218, 356

Ifenprodil, 39 Imidazole, synthesis, 246, 249, 254 tautomerism, 243 Imidazoline synthesis, 256 Imidazolinone synthesis, 260 Imidazolone synthesis, 291 Imidoline, 259 Imipramine, 420 Indapamide, 349 Indazole synthesis, 350 Indoles, as starting material for benzodiazepines, 405 Indomethacin, 345 Indoramin, 344 Indoxole, 254, 340 Inflammation, 63 Influenza A, 18 Inhibition, of cholinesterase, 294 of DNA gyrase, 370 of DNA synthesis, 12 of dopamine βhydroxylase, 279 of MAO, 266 of monoamine oxidase, 7, 27 of phosphodiesterases, 379, 464 of prolactin, 479 of sympathetic transmission, 100 Insertion reaction, 27 Interferon, inducer, 219 Intrazole, 345 Intriptyline, 223 Ipronidazole, 244 Isobuzole, 272 Isocarboxazid, 266 *Isoetharine,* 9 Isolectronic groups, 253 *Isomylamine*, 11 Isoniazid, 266 Isoproterenol, 37, 107

Isoxicam, 394 Ivanov salt, 68 *Ketamine*, 16 *Ketazocin*e, 328 Ketoprofen, 64 β-Lactamases, 442 Leniquinsin, 363 *Lenperone*, 286 Leprosy, 111 *Lergotrile*, 480 *Letimide*, 393 Leucine enkephalin, 317 *Lidocain*e, 95, 449 *Lifibrate*, 103 β -Lipotropin, 317 Lithium dimethyl cuprate, 4 *Lobendazole,* 353 Lometraline, 214 Lomustine, 12, 15 Loperamide, 334 Lorbamate, 21 Loxapine, 427 LSD-25, 476 Lucanthone, 413 Luteolytic activity, 6 Lysergic acid, 475 *Mafenide*, 114 Mannich reaction, 17, 40, 45, 57, 155, 223, 233, 234, 261, 336, 362, 410, 454, 456 MAO, see monoamine oxidase Maprotiline, 220, 221 *Mazindol,* 462 *Mebendazole,* 353 *Mebeverin*e, 54 MeCCNU, 12 Meclocycline, 227 *Meclofenamic acid,* 88 Medibazine, 30 Mediquox, 390 Medroxyprogesterone

acetate, 165 Medrysone, 200 Mefenamic acid, 280 Mefenorex, 47 Mefexamide, 103 Melitracin, 220 Melphalan, 120 Memotine, 378 Menoctone, 217 Meperidines, 328 reversed, 331 Meprobamate, 21 *Mesuprin*e, 41 Metabolic activation, 464 Metabolism, of steroids, 138 Metalol, 41 Metformin, 20 Methacycline, 227 Methadone, 328 Methionine enkephalin, 317 Methisazone, 350 Methixene, 413 17-Methyltestosterone, 156 Methynodiol diacetate, 149 Methysergide, 477 Metiamide, 252 Metiapine, 429 *Metizolin*e, 256 Metolazone, 384 Metoprolol, 109 Mexenone, 175 Mianserin, 451 Mibolerone, 144 *Miconazole, 249* Midaflur, 259 Migraine, 477 Milipertine, 341 Mimbane, 347 Mineralocorticoids, 177 *Minocycline, 228* Mixed agonists-antagonists, 318 Mixidine, 54 Modaline, 299 Molecular dissection, 9,

17, 96, 237, 315, 325, 449 *Molinazone,* 395 Molindone, 455 Monoamine oxidase, 7, 49 Moprolol, 109 Morazone, 261 Morphine, 314 Morphine rule, 17, 328 *Moxnidazole, 246* Nadolol, 110 Nafenopin, 214 Nafomine, 212 Nafronyl, 213 Nalbuphine, 319 Nalidixic acid, 370, 469 Nalmexone, 319 *Nalorphine*, 318 Naloxone, 318, 323 Naltrexone, 319 Naranol, 454 Nef reaction, 2 Nefopam, 447 Nequinate, 369 *Nexeridin*e, 17 *Nicergoline*, 478 *Niclosamide,* 94 *Nifedipine, 283* Nifuratrone, 238 Nifurdazil, 239 Nifurimide, 239 Nifuroxime, 238 Nifurpirinol, 240 *Nifurquinazol, 383* Nifursemizone, 238 *Nifurthiazole, 241* Nimazone, 260 *Nimorazole,* 244 *Niridaz*ole, 269 Nisobamat**e**, 22 *Nithiazole, 268* Nitronic acid, 2 *Nivazol,* 159 Nocardicins, 435 Noracymethadol, 58

Norbolethone, 151 Norepinephrine, biological effects, 38 Norethindrone, 145 Norgestrel, 151 19-Nortestosterone, 142 Nucleophilic aromatic substitution, 64, 65, 79, 89, 95, 281, 282, 406, 410, 413, 425 Octazamide, 448 Octriptyline, 223 Opium, 314 Organoboranes, amination, Ormetoprim, 302 Oxamniquine, 372 Oxantel, 303 Oxaprozin, 263 Oxazepam, 402 Oxazole synthesis, 263 Oxazolinone synthesis, 246, 265 Oxfendazole, 353 Oxibendazole, 352 Oxidation, metabolic, 464 microbiological, 160, 180, 183, 196, 373 by nitroalkanes, 28 with ruthenium tetroxide, 404 Oxilorphan, 325 Oxiperomide, 290 Oxisuran, 280 Oxolinic acid, 370, 387 Oxprenolol, 109 Oxyfedrine, 40 Oxymorphone, 319 Oxypertine, 343 Oxyphencyclimine, 75 Oxyphenisatin, 350 Oxytetracycline, 226 Pancuronium bromide, 163

Papaver bracteatum, 319 Papaver somniferum, 314, 318 Paraaminosalicylic acid, 89 Paranyline, 218 Parapenzolate bromide, 75 Parasympathetic nervous system, 71 Pargyline, 27 Parkinson's disease, 52, 119 Pazoxide, 395 Pemerid, 288 Penfluridol, 334 Pentapiperium methylsulfate, 76 *Pentazocin*e, 325 Pentoxifylline, 466 Perhydropyrindene synthesis, 450 Perlapine, 425 Pharmacophore, 233, 237, 242, 255, 278, 361 Pharmacognosy, 466 Phenbutalol, 110 Phencarbamide, 97 Phenmetrazine, 261 Phenyl aminosalicylate, 89 Phenylbutazone, 388, 474 Phenylephrine, 265 Phenylpiperidinols, 334 Physical dependence, 314 Pill, the, 137, 164 for canines, 144 *Pimetine,* 286 Pimozide, 290 *Pind*olol, 342 Pinoxepin, 419 Pipamperone, 288 Pipobroman, 299 *Piposulfan, 299* Piprozolin, 270 *Piquizil*, 381 Pirandamine, 459

Pirbuterol, 280 Piromidic acid, 470 Pirprofen, 69 *Pizotylin*e, 420 Poldin**e**, 74 Poldine methylsulfate, 74 Polonovski reaction, 240, 402 Potassium canrenoate, 174 Potassium m**ex**renoate, 175 Potassium prorenoate, 175 Poultry, epidemics in, 366 *Practolol*, 106, 108 Pranolium chloride, 212 Prazepam, 405 Prazosin, 382 Prednisolone, 178 Prednival, 179 *Probuco1*, 126 Procarbazine, 27 Prodolic acid, 459 Prodrug, 48, 50, 89, 198, 363 Progesterone, 164 Proglumide, 93 Propanidid, 79 Propenzolate, 75 Propizepine, 472 Propoxyphene, 57 Propranolol, 105, 107, 212 Proquazone, 386 Proquinolate, 368 *Prorenon*e, 175 Prostalene, 5 *Pr*oxazole, 271 Purine synthesis, 467 Psilocybine, 342 Psychotomimetic activity, 71 Pyrantel, 303 Pyrazine synthesis, 298 Pyridazine synthesis, 304 Pyrimidine synthesis, 302, 467 Pyrinoline, 34 *Pyrovalerone*, 124

Pyroxicam, 394 Pyrroliphene, 57 Quazodine, 379 Quinate coccidiostats, 366-370 Quinazosin, 382 Quinbolone, 154 Quindonium bromide, 139 Quinolone synthesis, 363 Quinoxaline synthesis, 388 Quinterenol, 366 Reaction, time honored, 92 Rearrangement, Beckmann, 419 of benzisothiazoles, 393 Chapman, 89 cyclopropylcarbinyl, 223 Fries, 42, 43, 355 glycidic ester, 374 Hofmann, 49, 117, 279 isoxazole to cyanoketone, 159 lactone-amide, 282 ring exchange, 236 Smiles, 430 Stevens, 124 Wagner-Meerwein, 323, 347 Receptors, α-, 105 α -adrenergic, 37 β-, 105 β -adrenergic, 37 as drug targets, 50 for opioids, 316 Reductive alkylation, 47, 55 Reformatsky reaction, 209, 355, 424, 460 Retro-Claisen reaction, 49 Rigid analogues, 50, 223, 284, 296, 451 Rimantadine, 19 Rimiterol, 278

*Risocain*e, 91 Ritodrine, 39 Ritter reaction, 19 Robinson annulation, 224 *Rodocain*e, 450 Roletamide, 103 Rolicyprine, 50 Rolodine, 468 Ronidazole, 245 Rotoxamine, 32 Salbutamol, 280 Salsalate, 90 Sapiens, homo, 316 Semustine, 12, 15 Serotonin, 96, **34**3 Serum cholesterol, 56, 78, 161 Slow release drugs, 143 Solypertine, 342 Sotalol, 41 Soterenol, 40 Spirilene, 292 Spironolactone, 172 Stenbolone acetate, 155 Strecker reaction, 119 Streptokinase, 377 Sudoxicam, 394 Sulazepam, 403 Sulfabenzamide, 112 Sulfacytine, 113 Sulfanilamide, 112 *Sulfanitran,* 115 *Sulfapyridin*e, 114 *Sulfasalazine,* 114 Sulfazamet, 113 Sulfonamide diuretics, SAR, 87 Sulfonterol, 42, 43 *Sulindac*, 210 Sulnidazole, 245 Sulpiride, 94 Sulthiame, 306 Suprofen, 65 Symetine, 29 Sympathetic blocker, 363

Sympathetic nervous system, 36 Sympathomimetic, 47 agents, 36, 365 α - agents, 255 Taclamine, 224 Talampicillin, 438 Talopram, 357 Tamoxifen, 127 Tandamine, 347, 460 Tazolol, 110, 268 Teclozan, 28 Temazepam, 402 *Terodiline*, 56 Tesicam, 379 Tesimide, 296 Testolactone, 160 Tetrahydropyrimidine synthesis, 303 Tetrahydroquinoline synthesis, 371 Tetrazole synthesis, 301, 345 Tetrydamine, 352 Thalidomide, 296 Thebaine, 318 Thenium closylate, 99 Theobromine, 456 Theophylline, 464 Thiabendazole, 352, 353 1,2,5-Thiadiazole synthesis, 271 1,3,4-Thiadiazole synthesis, 272 Thiamphenicol, 45 Thiampirine, 464 Thiazole synthesis, 240, 269 Thiazolinone synthesis, 270 Thienamycin, 435 Thioguanine, 464 Thiothixene, 412 Thioxanthone synthesis, 400

Thozalinone, 265 Thyromedan, 79 Thyroxine, 78 Tibolone, 147 Tibric acid, 87 Ticarcillin, 437 Ticrunafen, 104 Tienilic acid, see ticryanfen Tigestol, 145 Tiletamine, 15, 16 Tilorone, 219 Timolol, 272 Tiquinamide, 372 Tofenacin, 32 Tolamolol, 110Tolazoline, 106 Tolindate, 208 Tolmetin, 234 Tolnaftate, 211 Tolpyrramide, 116 Torgov-Smith synthesis, 140 Tralonide, 198 Tramalol, 17 Tranexamic acid, 9 Tranylcypromine, 7, 50 Trazodone, 472 Treloxinate, 432 Triacetone amine, 288 Triamcinolone, 185 Triampyzine, 298 Triazinedione synthesis, 305 Triazuril, 305 Tricetamide, 94 Triclonide, 198 Triflocin, 282 Triflubazam, 406 Triflumidate, 98 Trilostane, 158, 159 Trimazosin, 382 Trimethoprim, 302 Trimethoquinol, 374 Trimetozine, 94 Trimoxamine, 49 Trip, 476

Tryptamine, 343 Tybamate, 22 Ulcerogenic potential, 64 Ullman reaction, 413, 425, 428, 429 Urokinase, 376 Vasodilator, 30 Viloxazine, 306 Vilsmeir reaction, 189 Volazocine, 327 von Braun demethylation, 321 Whipworm, 303 Willgerodt reaction, 68 Wittig condensation, 3, 6 Wittig reaction, 420 Woodward hydroxylation, 215 Xipamide, 93 Xylamidine, 54 Xylazine, 307 Yohimbine, 347 Zolterine, 301

Errata for Volume One

In a work of this magnitude it is an unfortunate fact of life that errors will creep in. We are grateful to our friends and students who have enabled us to compare their lists with ours. Fortunately, the majority are typos and other grammatical mistakes that are embarassing but do not obscure the meaning nor the veracity of what we were conveying. These have been corrected in subsequent printings of the work and are not reproduced here. Those mistakes that are less obvious and/or which we feel might mislead those not familiar with the particular subject matter involved are listed here. The interested reader can annotate volume 1 accordingly. Every effort has been made to ensure that the number of mistakes that creep into volume 2 have been held to a minimum. It is hoped that the authors have the reader's understanding if not forebearance for those which remain.

Errata

Page	<u>Line</u>	<u>Old Entry</u>	New Entry
6	19	tropane.	tropane. ¹³
8	9	Hydrogenation	Cvanohvdrin reaction
8	11	ester, 19.	ester, 20.
11	Tab.	(X and Y for ambuca:	ine are reversed.)
16	3	(64)	(64a)
16	4	(65)	(65a)
16		Formula 64	64a
16		Formula 65	65a
17		Formula 74	(CH ₂) ₂
17	6	butylamine	propylamine
18	21	(85) via	(88) via
32	6	,36,	,39,
33	1	43,	42,
3 3	5	43,	42,
33	29	41	47
34	2	(7).	$(7).^{14}$
36	8	(8).	(8). ¹⁴
36	7	dicyclonime	dicyclomine
36	13	dihexyrevine	dihexyv e rine
38	last	clocental (25)	clocental (75)
42	14	-l-methylpyrro-	-l-methylpyrrolidine
		diline	
47	2	azacyclonol	pipradol
47	4	pipradol	azacyclonol
54		Formula 76	
			→ C1 {-s

514

66	2	pronethanol	pronethalol
66	4	soltalol	sotalol
67		Formula 6	(remove "6")
68		Formulas 37 and 38	(numbers are reversed)
70		Formula 51	(remove "51")
70	15	(54). ¹²	(54). ¹³
70	23	(58)	(59)
70	26	phenylbutanone-2	phenylpentanone-2
72	17	oxoethazine	oxoethazaine
74	7	fencamfine	fencamfamine
78	3	p-chloroaceto-	p-methylacetophenone
		phenone	
78		Formulae 109, 110,	(p-CH ₃)
		111	
86	2	isopropylbenzene	isobutylbenzene
86	15	alkylation of	alkylation with ethyl
			iodide of
86	16	base with ethyl	base affords
		iodide affords	
86	23	monoethyl	monomethyl
86		Formulas 1-5	CH ₃ -CHCH ₂ -
90	5	dimethylamine	diethylamine
90	6	carbetapentane (39)	(38)
90		Formula 38	38, $X=N(C_2H_5)_2$
91		Formula 44	() ()

92	6	cyclopyrazolate	cyclopyrazate
9 3	11	benactizine	benactyzine
96	10	phenol, 77.	phenol, 77a.
96	13	of 77	of 78a
9 6	15	ether (79).	e ther (79a).
96	19	of 79	of 79a
97	4	(80) to afford	to afford
97		Formula 77	77a
97		Formula 78	78a
97		Formula 79	79a
97		(Unnumbered formula	should be 80)
100	15	, 2 , ²	,2, ¹
102		(Formula 7 is super	fluous and should be
		removed.)	
111		Formula 16	Х=Z=CH ₃ ; Y=H
111	17	of 21	of 20
111	18	hydrazone (24)	hydrazone (23)
115	5	(42).9,10	(43).9,10
116	2	moxysylyte	moxisylyte
117	last	(66). ¹⁹	(66). ¹⁸
119		Formulas 76 and 75	(convert Cl to CH3)
120		Formula 81	
			R OCH ₂ CO ₂ H
123		(Compound 94 should	be spelled sulfaproxy-
		line.)	
136	4	19 3 0s	1920s
137	3	piperidine	azepine
137	7	tolazemide	tolazamide

Errata

137		Formulas 190, 191, 19 3	€— N
138	3	carbutemide	carbutamide
138	5	1-buty1-3-metany1-	l-butyl-3-meta-
		urea	nilylurea
141	9	thiazosulfone	thiazolsulfone
150		Formula 29	
151	17	amytriptylene	amitriptyline ^{CH} 3
151	23	methylpipyridine	methylpiperidin e
152	6	tylene	tyline 🔀
153		Formulas 45/46	OCH3
172		Formula 78b	(Replace angular Me
			group by H but leave formulae 78a and 78c alone.)
173		Formula 80	
174	7	eneone (91)	eneone (95)
175		Formula 92	(Also remove arrow
			from 91.)
			ОН
			H-H
			5

176 3	3 9	(109),	(107),
180		Formula 124	OCO(CH ₂) ₄ CH ₃
183		Formula 145	
186 Ta	ab.	norethinodrel	norethynodrel
19 3		Formulas 174 and 175	(Renumber to 174a and 175c)
196 2	21	N-bromosuccínide	N-bromosuccinimide
196-7		Formulae 192-198	
198		Formulae 205-207	
199		Formulae 211-212	
200		Formula 219 J	Aco Aco F
203		Formula 240	OH instead of OAc
213		Formulae 1-3	i H-
213		Formulas 9 and 10	CONH ₂
219		Formulas 3 and 4	H ₃ C CH ₂ OCOX
225		Formula 47	CONHCH ₂ CH-5

224		(Unnumbered formula	is 41.)
231	last	gives nifurprazine	gives the thiadiazole
		(46). ¹³	analogue (46) of
			nifurprazine (46a). ¹³
232		Add formula 46a	N=N.
		0 ₂ N-	COM CH= CH-NH2
233	8	isocarboxazine	isocarboxazid
233		Formula 50	(Reverse the methyl
			and allyl groups.)
234	18	reduction affords	reduction and methyl-
			ation affords
234	19	(61),	(61a).
235		Formula 68	$CH_3(CH_2)_3CH(CO_2C_2H_5)_2$
235		Formula 61	^R 2 ^N ^{CH} 3 61, R=H
			\searrow 61a, R=CH _z
		CH	
241		Formula 95	3
			SH
242		Formula 101	1
			CH ₂ -CH ₂ -COCH ₃
			NH
242		Formula 102	H
		<u></u>	
246	4	(132);	(130);
246	2	acetophenone	propiophenone
246	last	tetratoin	tetrantoin

246		Formulae 130-133	C₂H₅−C
247	10	aminitrazole	aminitrozole
249	27	ambient	ambident
257	9	glutethemide	glutethimide
257	12	aminogluthemide	aminoglutethimide
260	6	guancycline	guanacline
263	6	(71).	(7la).
263	8	(72).	(72a).
263	(Ren	umber formulas 71 an	d 72 to 71a and 72a.)
263	(An	arrow should connect	formulas 73 and 74.)
264		Formula	HN Num CH CH CH
			H _o N
264		Formulas 75-79	J−N CH CH CH
			CH ₂ CH ₂ CH ₃
			}—N
265	8	uracyl	uracil
265	12	uracycls	uracils
266	15	(92). ²⁸ (94), ²⁹	(94). ²⁸ (95), ²⁹
266	1	amisotetradine	amisometradine
265	last	aminotetradine	aminometridine
269	1	105	105a
269		entry 110	сн ₃ снсн ₂ сн ₂ сн ₃
270	6	allilic	allylic
262	2	phenylacetonitrile	p-chlorophenylaceto-
			nitrile
262		Formulas 63-65	(add a p-chloro group)
272		Formula 124	H ₅ C ₂ NH
			C _a H _r CH
			H ₂ C ₁ H ₁
			S U NM

278	19	171.	171a.
279		Formula 171	171a.
281		Formula 182	NH
			{ — nнСnн ₂
287	last	(4).	(4). ²
295		Formula 30	40 (also remove +)
301	1	furfuryl	tetrahydrofurfuryl
301		Formulae 82-85	-CO ₂ C ₂ H ₅
301		Formulae 85-87	
305	7	prolidine	prodilidine
308	20	pirintramide	piritramide O OCH ₇
315		Formula 14	щ L
			3 CH ₂
316	15	predominate	predominate. 5
318	last	scision	scision.
3 19	5	Rawaulfia	Rauwolfia
320	13	fused to	fused α to
320	17	potassium per-	potassium chlorate
		chlorate	. 1
320		Formulas 30-32	
321	7	synthesis.	synthesis. ¹² OCH-
322		Formulas 47-49	R CO
			()
			$_{C1}$

325	13	clonitazine	clonitazene
325	14	etonitazine	etonitazene
327	3	ethoxysolamide	ethoxazolamide
333	last	salicylaldehyde	acetophenone
334		Formulae 21-30 shou	ld have a CH ₃ group
		instead of Has 30 is	
335	13	,35,	,35a, CH _z
336		Formula 35	35a
336	8	the bronchodilator	the antiasthmatic
336	9	its extremely	its disodium
		insoluble disodium	
337		Formulas 46 and 47	-CHOH-
338	23	cincona	cinchona
340	10	59.	59. 13
343		Formula 76	76a
346	15	,101.	,103.
346	19	(103) affords	(101) affords
348	13	same	name
352	8	diethylamine	piperidine
352		Formula 138	<i>ţ</i> −N

355	29	anthralic
355	30	anthranillic
356		Formula 163

anthranilic acetic anhydride

N H NH ļs-0₂

1

358		Formula 182	A
358		Compound 179	ethiazide
3 59	1	trichlomethiazide	trichlormethiazide
3 59	7	cyclopentadiene.49	cyclopentadiene.44
359	2	althizide	althiazide
35 9	16	altizide	althiazide
365	13	the oxime	the N-methyl analogue
			of the oxime
365		Formula 14	N-CH3
366	7	of diazepam	of desmethyldiazepam
368	22	amide (37).	amide (36).
368	25	The N-methylated	Intermediate 15
		analog of inter-	contains
		mediate, 15, contain	ns
370	1	cloxazepam	cloxazolam
373	28	of 3,	of 1,
376		Formula 22	COCH ₂ CH ₂
379	1	(30)	(31)
380	-	Formulas should all	have $CH_{\alpha}CH(CH_{\alpha})N(CH_{\alpha})$
		as the side chain.	
386	6	piperactizine	piperacetazine
3 89	8	of the methylthio-	of substituted
		substituted	
389	8	phenothiazine with	phenothiazine 113 with
3 89	10	(115). ¹⁹	(114). ¹⁹

Errata

389	14	(114)	(115)
3 89		Formulae 112, 11 3	-SCH3
		and 115	5
3 90	5	pyrrolidyl	piperazinyl
3 90	9	at the expense of	in favor of
3 90		Formulas 118 and	_
		120	f-N
3 90		Formulas 117 and	-N(CH ₃) ₂
204	F	119 proponthe	nronanthou
301	34	catalvet	Cataluct 3
400	5 1 7	thiothivine	thiothivene
400	,	Eormula 42	
401		FOIMUIA 42	$-N$ $N - CH_3$
404	10	amytriptyline	amitriptyline
405		(The unnumbered for	mula should be 76)
405	10	dibenzepine	dibenzepin
410	32	4, a	4, ¹ a
410	36	phenbencillin	phenbenicillin
414	21	carb e ncillin	carbenicillin
414	17	amoxycillin (35)	amoxycillin (28a)
414		Formula 27,	NHR
414		R=CO ₂ CH ₂ C ₆ H ₅ , X=H Formula 28, R=X=H	х - Сн-;
414		Formula 28a, R=H, X	=OH
417	11	43.	43. ²⁴
426	10	oncolyltic	oncolytic

524
426	12	oxidate	oxidase
429	9	(39).	(39).8
430	2	(47); ¹⁰	(47); ¹¹

Changes To Be Made In The Index:

Althiazide	Ethoxzolamide
Aminitrozole	Etonitazene
Aminoglutethimide	Fencamfamine
Aminometradine	Flumethiazide
Amisometradine	Glutethimide
Amitriptyline, 151, 404	Guanacline
Benactyzine	Gaunochlor
Benzphetamine	Guanoxan
Betamethasone	Hydroflumethiazide
Biperiden	Iodothiouracil
Butallonal	Isocarboxazid
l-Butyl-3-metanilyl urea	Isoproterenol
Caramiphen	Levarterinol
Carbenicillin	Levalorphanol
Carbetidine	Mebhydroline
Carbutamide	M ephenoxalon e
Carisoprodol	Metaproterenol
Chlorimpiphenine	Metaxalone
Chloropyramine	Methaphenilene
Chlorotrianisene	Methdilazine
Cromoglycic acid	Methyclothiazide, 360
Clonitazene	Methylthiouracil
Cloxazolam	Methyridine, 256

525

Errata

Cyclopyrazate Debrisoquine Desipramine Dexamethasone Dicyclomine Dihexyverine Dimetacrine Dipiproverine Dithiazanine Etriptamine Ethacrynic acid Ethiazide Prolintane Pronethalol Propylthiouracil Prontosil Protriptyline PTU, see propylthiouracil Rescinnamine Sotalol (delete Sulfadiazene, 128) Sulfaproxyline Tetrantoin Thiomestrone Thiazolsulfone Trichlormethiazide Trifluperidol Trihexyphenidyl Tripelennamine Uracils

Moxisylyte Nikethamide Norethynodrel Nortriptyline Oxoethazaine Paraethoxycaine Pargyline Phenbenicillin Pholcodine Piperacetazine Piritramide Prodilidine

526